

SPECIAL REPORT

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EDWIN J. MEESE III CENTER FOR LEGAL AND JUDICIAL STUDIES

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Substance abuse disorders shackle users to a life devoted to reliving a fleeting euphoria or avoiding a deep abyss. Psychedelics hold promise for people who suffer from those disorders, as well as others such as depression or post-traumatic stress. Science certainly should continue its recently reinvigorated investigation of the potential benefits of this category of drugs, but we must be sure not to let our desire to learn whether psychedelics truly are therapeutic, at a cost that society is willing to bear, blind us to what the results of those inquiries reveal or don't yet tell us. Here, as elsewhere, we should remember that there might have been eminently sensible reasons why a particular category of drugs was outlawed.

“To be shaken out of the ruts of ordinary perception, to be shown for a few timeless hours, the outer and inner world, not as they appear to an animal obsessed with survival or to a human being obsessed with words and notions, but as they are apprehended directly and unconditionally by Mind at Large—this is an experience of inestimable value to everyone and especially to the intellectual.”

—Aldous Huxley, *The Doors of Perception* (1954)

“Chemically induced hallucinations, delusions and raptures may be frightening or wonderfully gratifying; in either case they are in the nature of confidence tricks played on one's own nervous system.”

—Arthur Koestler, “Return Trip to Nirvana,”
from *The Sunday Telegraph* (1967)

“If it [a psychedelic]...helps people to die peacefully with their friends and their family at their side, I don’t care if it’s real or an illusion.”

—David Nichols, Purdue University chemist
and pharmacologist

Introduction

Mention the term “psychedelic” to a Baby Boomer, and you will trigger memories (and in some cases flashbacks) of hippies, tie-dyed T-shirts, rock-and-roll, cannabis, civil rights demonstrations, Vietnam War protests, and Woodstock.¹ The term would also bring to mind 1960s countercultural icons like Ken Kesey, Aldous Huxley, Hunter Thompson, and especially Timothy Leary.²

Leary, at one time a Harvard University psychology professor, aggressively touted the use of psychedelics as a means of “expanding” one’s mind by altering a person’s sensory perceptions and thoughts.³ He had quite an effect on popular culture, which rebroadcasted his utopian, messianic visions to people in their 20s and applauded his psychedelic use.⁴ (Think of the Beatles’ songs *Lucy in the Sky with Diamonds*,⁵ *Tomorrow Never Knows*,⁶ and *I Am the Walrus*;⁷ Jefferson Airplane’s *White Rabbit*;⁸ The Doors’ *Break on Through (To the Other Side)*;⁹ and the Grateful Dead’s *Black Peter*¹⁰ or movies like *Easy Rider*¹¹ and *Yellow Submarine*.¹²) Leary became the “pied piper” of one particular hallucinogenic drug: lysergic acid diethylamide, better known by its acronym LSD or nickname “acid.” He also became famous (or infamous; take your pick) for the line “Tune in, turn on, drop out.”¹³ Indeed, the use of psychedelics was the common denominator to every item mentioned above. “Although the matter was often obscured for tactical reasons, there is no doubt that the initiating element, the sacrament, the symbolic center, the source of group identity in hippie lives was the psychedelic drug trip.”¹⁴

For thousands of years, Native American tribes in the lower 48 states, people in the Amazonian Region, and others elsewhere used psychedelics for their psychoactive effect in religious ceremonies.¹⁵ Beginning in the 1950s, the medical profession became interested in psychedelics as a treatment for refractory mental disorders as different as alcoholism, depression, and schizophrenia.¹⁶ Psychedelic use was legal throughout the United States until 1966, and researchers published more than one thousand articles on their clinical results.¹⁷ Psychedelic use did not become a recreational activity until it “escaped” from labs onto college campuses in the 1960s,¹⁸ and

the trip ended in the 1970s. The drugs did not altogether disappear, but cannabis and cocaine became the principal drugs of choice because they had “reliably euphoric effects” and did “not alter consciousness too much.”¹⁹

Recently, there has been a renewed interest in the therapeutic uses of psychedelics. Researchers hope that they can enhance nervous system neuroplasticity (the ability to jettison old interneuronal connections and form new ones²⁰) and enhance a person’s ability to engage in blame-free introspection, potentially enabling individuals suffering from disorders such as depression,²¹ addiction,²² and post-traumatic stress disorder (PTSD)²³ to “unlearn” their self-destructive attitudes. If that were to occur, the benefits would be enormous.

The purpose of this *Special Report* is to summarize the arguments pro and con in the current debate about whether to legalize this category of drugs. The parts below will discuss the history of psychedelic use, the early scientific interest in their potential therapeutic uses, their decline and fall as legitimate treatment tools, the rebirth of research into psychedelics over the past two decades, and the arguments supporting and questioning the use of psychedelics as an adjunct to psychotherapy. The last part will offer some additional factors for consideration.

The bottom line is this: Psychedelic-assisted therapy (PAT)²⁴ has the potential to offer patients relief from otherwise debilitating and unrelievable conditions, but legalizing psychedelic use poses a goodly number of issues about the treatment’s potential benefits, harms, and the likelihood of their occurrence—issues that should be resolved before the drugs become mainstreamed. We might see answers to those questions in 2024 or soon thereafter. The reason is that pending before the U.S. Food and Drug Administration (FDA) is an application for approval of the psychedelic drug 3,4-methylenedioxymethamphetamine (MDMA, also known as “ecstasy” or “molly”)²⁵ for use in conjunction with psychotherapy as a treatment for PTSD.²⁶

One of the questions that the agency officials will ask themselves is: What are the proven and potential beneficial and adverse effects of psychedelics on patients in the short and long runs? Although the short-term results appear promising, one question is whether psychedelics can alleviate disorders such as PTSD, which afflicts a large number of Americans on a long-term basis, without also causing them long-term harm. Caution might militate in favor of awaiting the results of studies of the long-term use of psychedelics for treatment of chronic disorders—treatment that, following the strategy of the tortoise, not the hare, while potentially beneficial for some patients, could prove costly for others. Then there is the risk of

unsupervised recreational use, a problem aggravated by the lack of a Narcan-like medication that can immediately “turn off” a psychedelic.²⁷ Science might not provide a clear and easy answer in this case or in the ones that are likely to follow as different sponsors submit new applications to the agency for other psychedelics.

At the end of the day, the question is how to proceed in the face of uncertainty. For 80-plus years, America has entrusted the FDA to make that call, and it appears that the agency will make it again in the near future.

The Rise and Fall of Psychedelics

The term “psychedelic,” coined in 1956 by the psychiatrist Humphrey Osmond, comes from the melding of two Greek words: *psyche*, which means mind, spirit, or soul, and *delos*, which means manifest or clear.²⁸ Some psychedelics are organically based—such as psilocybin (a compound extracted from the *Psilocybe* genus of mushrooms that places the “magic” in those fungi);²⁹ mescaline (a substance found in the peyote cactus);³⁰ ayahuasca (a tea produced from boiling certain Amazon-basin plants);³¹ N,N-dimethyltryptamine (DMT, a plant compound); and ibogaine (a plant compound grown in Africa).³² Others are synthetic—such as LSD, ketamine (or “Special K”);³³ MDMA; and phencyclidine (PCP or “angel dust”).³⁴ Though similar, they are not identical; psychedelic drugs “have a vague family resemblance rather than an easily described set of features.”³⁵

Psychoactive drugs work on the brain in different ways. As Drs. Lester Grinspoon and James Bakalar put it, “[t]his topic has supplied volumes of eloquence.”³⁶ Their effect is far greater than what is experienced from cannabis. “Marijuana has been compared to walking a foot off the ground as opposed to the intergalactic voyage produced by LSD.”³⁷ Alternatively, cannabis has been “likened to a pony in contrast with the locomotive of mescaline.”³⁸ And if mescaline is a locomotive, what is LSD, given that it is “several thousand times as powerful as mescaline”?³⁹

Psychedelics distort our visual, auditory, and tactile interactions with the world or how we process them.⁴⁰ Psychedelics reshape “sensory, self, time and space perception” in a manner “alien to everyday experience.”⁴¹ Leary wrote that “[a] psychedelic experience is a journey to new realms of consciousness,”⁴² a journey also known by the slang term “tripping.” In his words, “[t]he scope and content of the experience is limitless, but its characteristic features are the transcendence of verbal concepts, of space and time dimensions, and of the ego or vanity.”⁴³ They “reset” or “reboot” the brain or help it form new interneuronal connections.⁴⁴ Psychedelics

also enable us to access unconscious or repressed memories.⁴⁵ In Jungian terms, psychedelics help to make “the unconscious conscious”⁴⁶ or elicit “a confrontation with the unconscious.”⁴⁷

Psychedelics attracted the interest of the American psychiatric profession in the 1950s.⁴⁸ One reason was that LSD’s hallucinogenic effects resembled symptoms of acute psychosis, such as visual misperceptions, thought disorders, and ego-dissolution, leading psychiatrists to hope that LSD could help treat psychosis or at least enhance their understanding of its origins.⁴⁹ A second reason was that after using a psychedelic, some test subjects felt “less depressed, anxious, guilty, and angry, and more self-accepting, tolerant, deeply religious, and sensually alert.”⁵⁰ Another interest was “using the powerful experiences of regression, abreaction, intense transference, and symbolic drama in psychodynamic psychotherapy.”⁵¹ Because the Swiss company Sandoz was willing to supply LSD to legitimate researchers and psychedelics could be lawfully distributed throughout the United States until the mid-1960s, research flourished.⁵²

Some of the hoped-for prospects, however, did not pan out. Initial tests revealed that LSD exacerbated the symptoms of schizophrenics.⁵³ Nonetheless, LSD research continued because the drug seemed to enable users to access repressed memories. For that reason, researchers thought that it might become a useful adjunct to psychotherapy for people suffering from otherwise untreatable disorders such as depression and addiction.⁵⁴ Unlike the schizophrenia-focused trials, those initial clinical trials seemed promising.⁵⁵ Some researchers believed that they might serve as valuable therapeutics that did not pose the risk of physical harm, dependence, or addiction; others were far less sanguine.⁵⁶ Although psychedelics were always controversial, their potential therapeutic uses were the subject of concentrated scientific examination during the 1950s and early 1960s.⁵⁷

Those hoped-for treatments ended in the 1970s. Contrary to popular belief, the end was *not* due primarily to the “war on drugs.”⁵⁸ Following the thalidomide tragedies in Europe, Congress tightened the pharmaceutical regulatory approval process early in the 1960s, making the application and clinical processes more rigorous and laborious than the practices governing the early trials.⁵⁹ Atop that, the European drug company Sandoz stopped providing LSD, the best-known psychedelic, to laboratories for research in 1965 because the firm concluded that Leary’s endorsement of recreational LSD use, along with reports of adverse effects such as psychosis and suicide, was damaging Sandoz’s reputation.⁶⁰ The result was to limit the amount of research being conducted.⁶¹

A handful of social factors also coalesced to turn society against those psychedelics.⁶² After becoming known and available to college students,⁶³ psychedelics led some novice users to experience “bad trips”⁶⁴ and appear in considerable numbers in hospital emergency rooms.⁶⁵ Also, the unsavory association of psychedelic use with the horrific crimes of the Charles Manson Family,⁶⁶ as well as the Central Intelligence Agency’s administration of psychedelics to servicemembers and civilians without their consent or knowledge as part of a research program into their effectiveness, stained this category of drugs without leaving any room for their short-term rehabilitation.⁶⁷ Finally, a massive increase in drug use in the 1960s led Congress to outlaw a host of drugs, including psychedelics, in the Controlled Substances Act of 1970 (CSA) by placing them in Schedule I, the category of drugs seen as dangerous, subject to abuse, and lacking any legitimate medical use.⁶⁸ The effect of that law has been to prohibit any physician from prescribing LSD for any purpose.⁶⁹ Psychedelics can still be approved for use in carefully supervised clinical trials, but obtaining approval for trial is a daunting affair, so federally funded clinical trials gradually disappeared.⁷⁰

The Resurrection of Psychedelics Research

In this century, psychedelics have become the subject of renewed interest. The hope is that they can serve as an adjunct to psychotherapy for certain intractable or “treatment resistant” disorders, such as PTSD, as well as for Substance Use Disorders (SUDs), whether due to nicotine, alcohol, or illicit drugs,⁷¹ or other purposes, such as improved psychological well-being or enhanced spiritual awareness.⁷²

The principal cause of psychological disability today is depression, particularly the worst form of that disorder, major depressive disorder (MDD).⁷³ Always sizeable,⁷⁴ the number of people afflicted by MDD has increased since 1990 due to population growth and enhanced longevity.⁷⁵ The U.S. Centers for Disease Control and Prevention estimates that 14 percent of American adults suffer from mood disorders, including depression, and that an estimated 300 million people worldwide are afflicted with that disorder.⁷⁶ Untreated depression can ruin a person’s mental health as well as adversely affect a person’s physical health in several ways: It can increase the rate of heart disease and diabetes, greatly reduce one’s daily functioning ability and quality of life, and—even worse—lead to suicide.⁷⁷ The cost of depressive disorders in this nation alone is also considerable with one rough calculation exceeding \$210 billion.⁷⁸

The FDA has approved more than 30 drugs for the treatment of depression,⁷⁹ but none provides a guaranteed cure. Those drugs provide no relief in 20 percent–40 percent of cases and have their own adverse side effects.⁸⁰ Research for new MDD treatments appears to have entered a “dark age” with no new major advance since Dwight Eisenhower was President.⁸¹ MDD therefore remains a relentless affliction.⁸²

Over the past few decades, researchers have re-examined psychedelics⁸³ to learn whether they can provide relief for treatment-resistant mental disorders.⁸⁴ The effect of plant-based psychedelics such as psilocybin—which have been used for millennia for their psychoactive effect in religious ceremonies⁸⁵ and were the subject of “intense scientific inquiry”⁸⁶ in the 1950s and early 1960s—has been known (anecdotally at least) for decades but is now under serious scientific investigation.⁸⁷ Synthetically produced hallucinogens—such as LSD—came along in the 20th century.⁸⁸ They also are being studied.⁸⁹ There have been a goodly number of clinical studies and meta-analyses of those studies investigating and discussing the potential therapeutic effects of psychedelics for various disorders, including addictive behavior.⁹⁰ More than 200 additional studies are underway.⁹¹

Some nongovernmental organizations devoted to the study of psychedelic medicine have come into being since this renaissance began.⁹² Several highly respected academic institutions in other countries—Imperial College London and Queens University in Canada⁹³—along with Johns Hopkins University; Mount Sinai Icahn School of Medicine; New York University Grossman School of Medicine; Stanford University; the University of California (Berkeley and Davis); University of Michigan; University of Texas at Austin; Washington State University; University of Wisconsin–Madison; and Yale—have created centers or programs for the study of psychedelic research.⁹⁴ Recognizing that this large number of investigations is underway, in June 2023, the FDA issued guidance to the scientific community regarding the conduct of psychedelic investigations.⁹⁵

Those drug trials have shown promise.⁹⁶ In 2019, the FDA approved the drug Spravato, a derivative of ketamine, as a Schedule III drug for use as a nasal spray for treatment-resistant MDD at a certified physician’s workplace.⁹⁷ FDA-approved clinical trials for medical use with counseling of other psychedelics are also currently underway.⁹⁸ For example, Johns Hopkins is researching the effects of psilocybin (a compound that creates a hallucinogenic effect) on depression, anxiety, PTSD, opioid-use and alcohol-use disorders, smoking cessation, anorexia nervosa, and obsessive-compulsive disorder, among other research projects.⁹⁹ That research seems promising. According to Bertha Madras, Professor of Psychobiology

at the Harvard Medical School, “[c]linical trials in the past several years have shown that one or two doses of psilocybin rapidly alleviated depressive symptoms, with therapeutic benefit lasting from 4 weeks to as long as 12 months.”¹⁰⁰ Australia has already approved the therapeutic use of two psychedelics—MDMA and psilocybin.¹⁰¹

There are developments in the United States. In 2017, the FDA granted breakthrough therapy designations¹⁰² for MDMA for the treatment of PTSD, and in 2018 and 2019, the FDA granted breakthrough therapy designations for psilocybin for use with treatment-resistant depression and MDD, respectively.¹⁰³ On December 12, 2023, a drug sponsor filed a New Drug Application (NDA) with the FDA seeking approval of MDMA as a treatment in combination with psychotherapy for PTSD.¹⁰⁴ The ongoing research into psychedelic medications and their subsequent approval could have value beyond the usefulness of these medications as a treatment for MDD, PTSD, and the like. The NDA tees up for the FDA the issue of whether MDMA, like ketamine, should be approved for treatment purposes.¹⁰⁵

Will New Zealand, Canada, Great Britain, the European Union, or the United States follow Australia’s lead? One or more of those nations might witness a groundswell of support for the proposition that the drug laws should be re-examined and revised to permit physicians to prescribe and supervise the administration of psychedelics for various psychiatric disabilities that currently approved pharmaceuticals cannot remedy. In this country, two states—Oregon and Colorado—have already revised their state criminal codes to permit the use of psilocybin for treatment purposes; others are considering the same option.¹⁰⁶ At the same time, a Congress that has proved itself unwilling to address our incoherent national cannabis policy¹⁰⁷—one where states can issue licenses to violate the federal controlled substances laws—is not likely to take up the legalization of psychedelics today, tomorrow, or even the days or months afterwards. But that day might come soon.¹⁰⁸

The medical and scientific communities are debating the therapeutic value of psychedelics. So far, the participants have migrated to one of two camps.¹⁰⁹ One believes that, under proper medical supervision and with necessary pre-treatment and in-treatment counseling, psychedelics can offer relief for select patients suffering from treatment-resistant disorders such as depression, PTSD, or addiction. The other camp is skeptical as to whether, because of shortcomings in early trials along with the lack of long-term studies of the effect of psychedelics on patients suffering from chronic disorders, the evidence known to date justifies administering psychedelics to patients.

The Arguments in Favor of Psychedelic Therapy

Several justifications, supported by a still-growing body of clinical studies, have been offered for psychedelic use. One is that psychedelics, in conjunction with psychoanalysis or some other form of “talk therapy,”¹¹⁰ can provide relief at minimal risk¹¹¹ for patients suffering from treatment-resistant psychological disorders, such as depression and PTSD,¹¹² or physiological ones, such as migraines and cluster headaches.¹¹³ A second justification is that psychedelics can help people—as they helped Bill Wilson, founder of Alcoholics Anonymous¹¹⁴—who suffer from substance abuse disorders to transition off drugs such as nicotine, alcohol, or heroin in multiple ways: by pruning neuronal connections that reinforce damaging learned behaviors, by retraining a user’s mind so that he or she can understand the self-destructive patterns of a life ruled by drugs,¹¹⁵ or by enhancing a user’s brain’s ability to develop new interconnections¹¹⁶ that enable the learning (or relearning) of healthy lifestyles.¹¹⁷ A third argument is that psychedelics help terminal patients overcome a sometimes suffocating “fear of death” and accept their mortality.¹¹⁸ A fourth justification is that psychedelics enhance users’ performance by enabling “more creative thinking,” which enables them to find “unconventional solutions.”¹¹⁹ A fifth justification is that psychedelics can enhance the lives of people who use them responsibly and that such an opportunity should not be deemed irrelevant or discounted to near zero.¹²⁰

It also appears that, when dispensed by physicians to patients under appropriate medical supervision during treatment, psychedelics appear to pose little harm to a user. Said in a more technical way, psychedelics have “a wide therapeutic index and favorable safety profile when administered in doses within the therapeutic range under controlled and comfortable settings.”¹²¹ Adverse effects have generally been mild or moderate in severity and were treatable.¹²² Effects such as dissociation (from ketamine) were not debilitating under proper supervision.¹²³

Advocates for the use of psychedelics realize that they have an uphill battle because drugs like LSD are currently in CSA Schedule I, which means that they cannot be prescribed for any non-research medical purpose. Two developments, however, have convinced advocates that they might be able to persuade the federal and state governments to change the law. One is the FDA’s 2019 approval of ketamine, a drug often abused as a “club drug” because of its dissociative effect.¹²⁴ The other development is the series of revisions that numerous state legislatures have made in their own laws to allow cannabis to be used for medical purposes.¹²⁵ Those facts have likely persuaded supporters of psychedelics that pursuing the liberalization of the laws governing psychedelics is not a quixotic goal.

The Concerns About Psychedelic Therapy

On the other hand, some commentators have various concerns about psychedelic use.¹²⁶ Skeptics have identified several features of past studies that limit their usefulness as a basis for drawing broad conclusions.¹²⁷ For example, critics have pointed out that initial clinical studies lacked a control group receiving a placebo, sample populations were too small and too uniform in their composition, and studies were too short and too recent to uncover potential long-term problems.¹²⁸ Those are legitimate points, and later trials addressed many of them. Nonetheless, certain issues are unresolved and require attention.¹²⁹

The Value of Double-Blind Studies. The first issue involves a problem with the nature of clinical tests of psychedelics. Double-blind drug clinical trials—studies in which neither the clinicians nor the subjects know who is receiving the test substance or a placebo—are the gold standard for measuring a pharmaceutical’s safety and effectiveness, yet it is difficult to conduct a truly blind study of the effects of psychedelics. Unlike antibiotics, psychedelics have an inherent ability to distort perception and cognition, which lets test subjects know whether they have received such a drug.¹³⁰ To obtain a subject’s informed consent to treatment, the physicians responsible for managing any clinical test would need to inform the subjects that they might receive a psychedelic drug. As a result, any group experiencing perceptual and cognitive distortion would know that they received one, while subjects not undergoing those experiences would realize that they did not.¹³¹

That difference creates a quandary. On the one hand, an inactive placebo “allows for better contextualization of any safety findings.”¹³² On the other hand, subjects receiving a placebo might experience a nocebo effect—that is, “a worsening [of] symptoms as a result of knowing that they did not get active treatment.”¹³³ The FDA suggests that sponsors might be able either to substitute “subperceptual doses of a psychedelic drug” or “other psychoactive drugs that mimic some aspects of the psychedelic experience”¹³⁴ for an inert placebo or use non-treating psychologists unaware of who received a psychedelic in a post-treatment analysis of its effects.¹³⁵ Those options, however, still might not do the trick over the long haul. The upshot is that there might be no realistic way to conduct a double-blind clinical study of psychedelics in the same manner that we would use for other drugs.

The Long-Term Effect of Psychedelics on Patients. Another issue is whether we need long-term studies of the effects of psychedelics on patients.¹³⁶ We do not yet know all of the potential problems that can result from their long-term use.¹³⁷ Drugs like psilocybin and ketamine increase a

person's heart rate and blood pressure, and the long-term physical effect of those drugs on a long-term user's cardiovascular system, for example, is unknown.¹³⁸ For some patients, psychedelics can replace one debilitating condition—depression—with another—acute or chronic psychosis¹³⁹ (although the incidence of those disorders appears to be quite rare).¹⁴⁰

Disorders such as MDD are chronic problems and, at least under our current knowledge, cannot be solved by a single dose of any approved treatment.¹⁴¹ Psychedelics also are not a silver bullet. They take effect quickly, but their effect fades over time, requiring repeated dosing on a regular basis to afford patients continued relief, as the FDA noted in its 2023 psychedelic guidance.¹⁴² Two scholars have written that MDMA, while valuable in the short run, might not be “suitable” for long-term use if users are also taking other illicit drugs and perhaps even if they are not.¹⁴³ Even a recent study finding that the drug MDMA showed value in treating PTSD recognized that long-term investigation is necessary “to assess durability of treatment.”¹⁴⁴

Some scholars have concluded that there is little physiological or psychological risk from long-term psychedelic use.¹⁴⁵ Nonetheless, reasonable people could also believe that long-term studies are necessary to learn the dose level that is safe and necessary for repeated treatments to be successful, for determining the appropriate intervals before redosing should be undertaken, and for learning whether such repeated dosing has adverse chronic physical or psychological effects on patients.¹⁴⁶ For example, the FDA has expressed concern that long-term psychedelic drug use could lead to a potentially serious condition involving thickening of the heart valves.¹⁴⁷ There also is the question of who, if anyone, should be excluded from psychedelic treatment, particularly on a long-term basis, because of, for example, a risk of suffering an adverse physical or psychological reaction.¹⁴⁸ The FDA will need to decide whether such long-term studies are necessary before it decides whether to approve psychedelics for therapeutic use.

Essential to the resolution of that issue are various subissues. What are the relative risks of short-term and long-term harm to patients from delaying the approval of psychedelics until we have studies of their long-term effects versus the risk of creating new problems by approving those drugs before we know the results of long-term studies? What is the relative importance of relieving disorders today versus that of avoiding chronic problems by waiting for proof as to the effects and side effects of long-term use of this category of drugs?¹⁴⁹ What is the likelihood of psychedelic users developing a tolerance to the drug with long-term use? Will it be necessary for those who do use psychedelics to escalate the amount they consume? What risks does that pose?¹⁵⁰ Do we need a Narcan-like “rescue” treatment

for adverse effects before we legalize psychedelics?¹⁵¹ Those issues should be identified, investigated, debated, and resolved.¹⁵²

In that regard, the FDA's decision to approve Spravato (esketamine) is not necessarily a "precedent" for the approval of all other psychedelic drugs or ones that have psychedelic-like effects. Each such drug should be examined independently.¹⁵³

The Relationship, If Any, Between the Sensory and Cognitive Disruptions Caused by Psychedelics and Their Therapeutic Effect. A third important but unanswered question is whether—and, if so, to what extent—the sensory and cognitive distortions produced by drugs like psilocybin are unavoidably tied to their potential therapeutic effect.¹⁵⁴ Some researchers have suggested that nonpsychedelic drugs might be able to activate the neural receptors necessary to provide relief, as an example, for depression without generating the psychedelic experience of drugs like psilocybin.¹⁵⁵ According to Dr. Nora Volkow, Director of the National Institute on Drug Abuse (NIDA), there is no firm conclusion either way: "There is evidence to suggest that psilocybin's therapeutic efficacy is tied to the mystical-type experiences it commonly precipitates," although that connection is "controversial."¹⁵⁶ In addition, psilocybin is but one of the potential psychedelics being considered, and what is true in the case of one might not be true for the entire class of potential treatments.

As the FDA has noted, some psychedelic drugs have been the subject of "numerous investigations, as documented in the published scientific literature," but not all of them have been as rigorously examined.¹⁵⁷ Those drugs should be subjected to "a full abuse potential assessment."¹⁵⁸ Decoupling "depression-ameliorating neuroplastic effects" from "the cognitive and sensory distortions" might eliminate or reduce safety concerns with respect to psychedelic drugs,¹⁵⁹ but that would not be possible if the latter are essential to achieve the former.¹⁶⁰ We might have to accept the bitter with the sweet, but we should find out whether that is true before we commit to this course. We also should find out whether nonpsychedelic receptor agonists might prove to be safe and rapidly acting antidepressants.¹⁶¹

The Combination of Psychedelics and Psychotherapy. Another issue is how psychedelic pharmacology and psychotherapy should be combined. Some believe that psychedelics do not themselves resolve a patient's mental disorder but enable psychotherapy to do that work.¹⁶² Rick Doblin, founder and president of the Multidisciplinary Association for Psychedelic Studies, has said that "[c]ritically, MDMA taken in isolation, without therapy, does not automatically produce a beneficial effect," adding that "[i]t's not the drug—it's the therapy enhanced by the drug" that addresses a patient's underlying problem.¹⁶³

Commentators have recognized, however, that psychedelics pose special risks that other drugs do not pose. There might be serious adverse effects from improper use. As Dr. Ben Sessa, a psychiatrist and psychedelics advocate, has acknowledged:

There is no doubting that the misuse of psychedelic drugs can cause harm (by definition). The psychedelic experience can certainly be frightening and disorienting for ill-prepared users. Feelings of panic and losing control can become overwhelming. For some people with pre-existing mental illness, especially those with psychosis, psychedelic use can trigger severe reactions. The concept of a “bad trip” is well documented by both users and non-users of psychedelics.¹⁶⁴

Doctors Lester Grinspoon and James Bakalar have made the same point:

The worst kind of psychological reaction is a fixed intense emotion or distorted thought that can seem like an eternity of hell; for example, remorse, suspicion, delusions of persecution or of being irreversibly insane. The metaphysical bad trip is a devastating extension of this in which everything is implicated in the drug taker’s misery, his wretched feelings are seen as revelations of the ultimate nature of the universe, and he experiences some version of what mystics have called the dark night of the soul.¹⁶⁵

Psychotherapy accompanying psychedelic use is offered as the solution to those problems.¹⁶⁶ As Dr. Sessa has explained, psychedelics are “non-specific amplifiers,” meaning that “any emotion, good or bad, benign or destructive, can be magnified to dramatic proportions.”¹⁶⁷ Qualified psychotherapists can help a patient address and understand those emotions or any perceptual distortions that arise during treatment.¹⁶⁸

If so, it is important to consider *how* psychedelic treatments should be carried out. Both the patient’s “set” (expectations) and the treatment’s “setting” (environment) are important to the success of psychedelic-assisted therapy.¹⁶⁹ “Twenty years of research has standardized the dosage of the drugs used in clinical trials, but the therapy component has not received similar scrutiny.”¹⁷⁰ Counseling is “often based on tradition rather than empirical evidence.”¹⁷¹

The treatment afforded clinical trial participants has involved far more than simply hooking a patient up to an IV drip and handing him or her a magazine. Participants are carefully chosen and receive exhaustive physical and psychological testing before any trial begins, in part to exclude anyone

suffering from a severe mental illness such as psychosis.¹⁷² Studies have made extensive use of psychiatrists and other mental health professionals to educate participants about the effects (for example) of psilocybin before receiving treatment and to have those professionals (or trained psychologists or other personnel) present or available during its course.¹⁷³ The testing or treatment has taken place in a comfortable, almost spa-like setting, sometimes with participants wearing sunglasses and listening to background music while undergoing treatment—all of which is designed to keep a psychedelic experience from going south.¹⁷⁴ “The general consensus of clinicians and scientists in the field,” two scholars have found, “is that it is important to have one or two trained persons present during a psychedelic session in order to keep patients’ attention focused inward, and to provide physical and emotional support during the session.”¹⁷⁵

There is a powerful need to decide precisely what the quantity and quality of that counseling should entail.¹⁷⁶ To start, skepticism is justified in concluding that psychedelic therapy will be provided only in spa-type settings rather than play out the same way that medical cannabis programs handed out that drug: in businesses with in-house physicians writing a recommendation for medical cannabis use to anyone with \$40 and enough time for a coffee-break-long interview with nothing more than a fast-food version of a physical or psychological exam.¹⁷⁷ That could spell serious trouble for some people. Psychedelics are not for everyone,¹⁷⁸ which is why serious clinical studies carefully screen potential participants to exclude any for whom psychedelics might be harmful.¹⁷⁹ In-treatment medical monitoring of a patient is also necessary to prevent adverse outcomes.¹⁸⁰

There is widespread agreement that pretreatment, in-treatment, and post-treatment counseling is valuable, if not necessary,¹⁸¹ but there are numerous questions that need answers. For example, it is unclear how the psychoanalysis accompanying psychedelics should proceed because we lack a consensus on its proper role, content, and importance. Is it necessary or merely valuable? If merely valuable, how valuable is it—that is, what is its marginal contribution to the overall treatment package? What counseling should psychotherapists offer patients? How should that counseling be conducted—that is, should therapists be present throughout a treatment in the same room? Or should they be in the same office or clinic, nearby but immediately available? Or can they be on-call? Can the appropriate psychotherapy be “protocolized” because the FDA might have difficulty giving blanket approval to a medication requiring psychotherapy that lacks a consensus-driven protocol? Is it possible to have a “placebo cohort” because, as a practical matter, the protocol would be different if

someone is or is not hallucinating? Should there be a 1-to-1 ratio between therapists and patients or should therapists be permitted to treat a larger number of patients at any one time? If so, what is the maximum reasonable ratio? What are the risks of illicit psychedelic use, with or without medical involvement, and the resulting harms? What risk should patients be allowed to bear? What are the risks and social costs that society should be forced to bear if we underestimate the potential adverse results?

Now turn to questions about the therapists. Who is qualified to serve as a treatment counselor? What is the risk that an inadequately educated and trained psychoanalyst will torpedo the value of psychedelic therapy? How do we guarantee that only qualified individual therapists are involved?¹⁸² How do we ensure that an adequate supply of qualified personnel is available?¹⁸³ The FDA's guidance on psychedelic drugs offers recommendations—such as using two observers during a treatment session with the lead monitor possessing “graduate-level training and clinical experience in psychotherapy” as well as being “licensed to practice independently”¹⁸⁴—and researchers would be wise to consider them. But the FDA also notes that variability in the answers to the questions above presents a “challenge” for product labeling, which the FDA regulates.¹⁸⁵ Remember: The FDA regulates the interstate distribution of drugs; it does not license psychotherapists. That is in the states' bailiwick.¹⁸⁶ How, therefore, can the FDA ensure that dangerous drugs are not distributed to people who use unqualified therapists? And who should answer those questions—states, which regulate the practice of medicine,¹⁸⁷ or the FDA, which regulates the interstate distribution of pharmaceuticals?¹⁸⁸

Further complicating the issue is the development of telemedicine: the use of modern communication technology to obtain over the Internet a diagnosis and prescribed medication from a physician without any face-to-face meeting, let alone a physical examination.¹⁸⁹ Telemedicine would allow a physician in Maine to diagnose and treat a patient in Hawaii over a platform like Skype that he doesn't know and will never treat again.¹⁹⁰ Even if Hawaii finds that practice hunky-dory, the federal government might disagree. It could refuse to reimburse the prescription of psychedelics by telemedicine whenever Medicare or Medicaid is responsible for payment. The federal government also might be able to regulate that practice even when Medicare or Medicaid does not foot the bill by invoking its authority over interstate commerce,¹⁹¹ which includes the use of the facilities of interstate telecommunications to complete credit card transactions.¹⁹² The federal government might be able to stop a patient from receiving psychedelics even if he is treated in-person by a local physician and pays

for the treatment in cash if the drug has traveled in interstate commerce.¹⁹³ Those issues, however, are yet to be decided.

Regardless of how those issues are resolved, there is yet another one: the risk that patients will seek treatment from multiple physicians to obtain multiple prescriptions for psychedelics. That was one of the problems we saw during the opioid epidemic: Patients obtained multiple prescriptions for narcotics from different physicians because there was no way for each doctor to know what others had prescribed.¹⁹⁴ Telemedicine means that we could see the same outcome here. The result is that, absent a federal law or nationwide practice of collecting and sharing psychedelic prescriptions, perhaps one that is similar to the system now in effect for opioids—the Prescription Drug Monitoring Program¹⁹⁵—some patients might obtain and use more of those drugs than is safe or might use them at home without any direct medical oversight.¹⁹⁶

At the end of the day, it is likely that the states might be responsible for answering many, if not most, of those questions. Historically, the states have the responsibility for regulating the practice of medicine, while the federal government has the authority to decide what drugs may be shipped in interstate commerce. Once the FDA approves that shipment, the states regulate how a physician may use it as part of his or her professional judgment when treating a specific patient. That is why the co-called “off-label” use of a medication—viz., the use of a medication for a purpose not identified on its FDA-approved label—is generally permissible. Private insurers also have a say in how a drug should be administered because they decide what treatments are covered and reimbursable.¹⁹⁷ The FDA might not be able to address those problems on its own, but it might solicit the assistance of the states and private insurers, who might not all agree on what is the best resolution. Regardless of how those issues are resolved, the appropriate safety and ethical rules for psychedelic treatment should be defined and in place before the treatment is rolled out.¹⁹⁸

In this regard, discussions about that regulation must involve some consideration of how treatment protocols can and will be enforced. Standards without penalties for noncompliance are just advice, not rules. We could, of course, rely on the tort system to provide governing rules in the standard after-the-fact fashion that malpractice damages actions have traditionally served. It would be preferable, however, for patients, physicians, therapists, and pharmaceutical companies to have the guidelines resolved *ex ante* rather than *ex post*. Here, too, the federal and state government might need to work with the private parties just mentioned to hammer out reasonable conventions in the pre-FDA approval period.¹⁹⁹

One tool that the FDA can use as part of the drug approval process is to require a drug distributor to adopt a Risk Evaluation and Mitigation Strategy (REMS)—“a drug safety program...for certain medications with serious safety concerns” that is designed “to help ensure the benefits of the medication outweigh its risks.”²⁰⁰ For example, one long-lasting antipsychotic drug carries a risk of “serious” post-injection reactions called “post-injection delirium sedation syndrome.”²⁰¹ The symptoms include “feeling sleepier than usual (sedation), coma, and feeling confused or disoriented (delirium).”²⁰² The rationale for requiring a REMS is “to ensure that the drug is administered only in certified health care facilities that can observe patients for at least three hours and provide the medical care necessary in case of an adverse event.”²⁰³ Here, the FDA could require a psychedelic drug distributor to have a REMS that the agency finds is sufficient to address all of the issues discussed above regarding the need for an appropriate setting for administration of the drug. In particular, the FDA could limit pharmaceutical companies’ distribution of psychedelics to those physicians with REMS that the FDA finds satisfactory.²⁰⁴

The failure to comply with a REMS potentially exposes a physician to more than civil liability. The U.S. Department of Justice recently persuaded a grand jury to indict two physicians for allegedly illegally administering ketamine to patients and billing Medicare for that treatment because the physician licensed to distribute ketamine was not an active participant in the treatment.²⁰⁵ The result is that the federal government might have some valuable tools that it can use to police the actual practice of medicine, at least where the federal government is billed for it.

Additional Considerations

There are a few additional considerations worth noting.

Federal vs. State Regulatory Authority. With only two statewide exceptions—Oregon and Colorado²⁰⁶—the United States has addressed the issue of whether to approve psychedelic therapy by following the approach that the nation has used for 85 years to measure the safety and effectiveness of a new drug: Leave the responsibility to answer those questions with the FDA. Congress made that decision in 1938, and since then, that approach has become the traditional, settled, and legally and socially accepted model for recognition of new drugs.²⁰⁷

That process is underway. In 2019, the FDA approved the drug Spravato, an isomer (esketamine) of the dissociative drug ketamine, for use in treating MDD.²⁰⁸ The FDA also approved clinical trials for psilocybin and MDMA.

What is more, as noted above, the FDA has a pending application seeking approval of MDMA as an adjunct to psychotherapy.²⁰⁹ The agency will review the studies submitted by the sponsor, along with the other materials in the sponsor's application, and make its decision in due course. Whatever the FDA's decision on that application might be, one promising result of current events to which the nation appears willing to adhere is the traditional practice that the country has long used for the evaluation of the safety and usefulness of a new drug. That allocation of responsibilities is an important one because there are numerous factors that the FDA should consider in making its determination; it has the medical and scientific experts qualified to make drug safety judgments, while the states do not; and the judgments the FDA makes have important public health consequences.

That regulatory model is far preferable to the approach that society has witnessed playing out over the past three decades with respect to the legalization of cannabis.²¹⁰ Since 1996, numerous states, with California in the lead, legalized cannabis for medical use without waiting for the FDA to find that the botanical cannabis is safe, effective, and uniform and without independently performing (or requiring sellers to complete) any of the rigorous studies that the FDA would demand before legalizing a new drug for interstate distribution.²¹¹ A result has been the large-scale distribution of botanical cannabis that the FDA could not find qualifies for interstate distribution for a host of reasons, such as the possibility that it could be adulterated with multiple dangerous contaminants and the likelihood that it would vary greatly both in its ingredients and in the amount of its psychoactive content.²¹² The public is therefore exposed to a variety of cannabis products, in various forms, that have not been found to be safe, effective, and uniform as federal law requires.

The decision by Oregon and Colorado to authorize the use of psychedelics for medical treatment raises serious questions about whether the law is outpacing the science.²¹³ Those decisions also run headlong into the governing federal law: the Controlled Substances Act. Federal law deems psychedelics like LSD to be Schedule I drugs, which no physician may prescribe,²¹⁴ so administering psychedelics to a patient outside of federally approved clinical studies would be a federal offense regardless of what state law provides.²¹⁵ Accordingly, unless and until the FDA approves the use of psychedelics (and the Drug Enforcement Administration reclassifies those drugs out of Schedule I), Oregon and Colorado are just daring the federal government to stop their programs in the hope that their state congressional delegations will raise such a ruckus that the U.S. Department of Justice will back off prosecuting physicians for what appears to be federal crimes.

The federal government’s investigation of medical-use cannabis led Congress, beginning in 2015, to intervene through appropriations riders barring the federal government from “prevent[ing]” states from “implementing” state medical cannabis programs.²¹⁶ Oregon and Colorado might well be taunting the federal government to knock the chips off their shoulders in the hope that the public will have the same adverse reaction here as it did in the case of cannabis and persuade Congress to say *no mas*.

But even if Congress were not to follow that path—if only because there is no groundswell of public support for legalizing psychedelics, and certainly nothing that compares with the public attitude toward cannabis—the law as it stands now still gives rise to a problem. Consider the regulatory status of the dissociative drug ketamine. As noted above, in the 1970s, the FDA approved one isomer of that drug (esketamine) for use as an anesthetic, and in 2019, the agency approved that isomer as a nasal spray for treatment-resistant depression.²¹⁷ Physicians therefore can prescribe it for other purposes—the “off-label” use of that drug—without always or automatically violating federal law.²¹⁸

Yet, in 2022 and 2023, the FDA issued separate warnings about the misuse of the FDA-approved ketamine, isomer Spravato.²¹⁹ The agency noted that the drug had been “compounded” and distributed for the unsupervised, at-home use contrary to the warning that the FDA requires be placed on the drug.²²⁰ The FDA noted that it had approved ketamine for use in limited circumstances and that use otherwise, as seems to have occurred,²²¹ could lead to potentially serious physical and psychological problems.²²² Nonetheless, because the FDA approved ketamine in the 1970s for use as an anesthetic, physicians can prescribe it for other purposes.²²³ In 2023, the FDA issued its second notice²²⁴ warning about the misuse of ketamine, noting that the drug had been “compounded” and distributed for the unsupervised, at-home use contrary to what the FDA had authorized.²²⁵

In one recent case, ketamine was designated as the cause of the death of the actor Matthew Perry, a cast member of the well-known television show *Friends*.²²⁶ His death was initially reported as “an apparent drowning,” but “according to an autopsy released by the County of Los Angeles Department of Medical Examiner,” Perry died of “[a]cute effects of ketamine.”²²⁷ He “reportedly received ‘ketamine infusion therapy for depression and anxiety,’” but “[h]is last known treatment was more than one week prior to death.”²²⁸ The medical examiner determined that although “[t]he exact method of intake in Mr. Perry’s case is unknown,”²²⁹ the amount of ketamine in his system at death could not have resulted from that therapy because ketamine’s half-life is three to four hours (or less),²³⁰ and Perry’s

blood contained an amount of ketamine equivalent to what would be found during general anesthesia.²³¹ Accordingly, the FDA might decide that it is important to continue our investigation into the long-term effects of therapeutic psychedelic use and consider whether there should be reasonable but enforceable limitations on how much of a psychedelic drug a person should be allowed to use within a defined period.

Safety Considerations. Although researchers have attested to the safety of psychedelics when properly administered and supervised, psychedelics are potentially dangerous drugs even when used in a treatment setting, let alone recreationally.²³² Not everyone should use them, and the proper dosages must be identified.²³³ Even FDA-approved drugs like ketamine can have adverse effects,²³⁴ and people can endanger themselves or others by engaging in risky conduct while under their influence.²³⁵ The safeguards that accompany therapeutic administration of psychedelics will not protect someone who uses a psychedelic without medical supervision or recreationally. That is particularly true because we lack a Narcan-like “rescue” treatment for a psychedelic’s adverse effects.²³⁶

Aside from the risk of improper psychedelic use for medical purposes, ketamine has been used recreationally because of its short-term dissociative and hallucinogenic effects.²³⁷ Some individuals will be highly motivated to find a physician willing to prescribe psychedelics for that purpose, and, though we might wish it were not so, there is no rule of law or life guaranteeing that every physician will “do no harm.” On the contrary, the case law²³⁸ proves that not every physician has the scruples of *ER*’s Mark Greene.²³⁹ Moreover, legalizing psychedelic use, even under responsible, close medical supervision, removes whatever stigma is associated with its current Schedule I status, thereby weakening a potential deterrent to illicit use.²⁴⁰

Justified Skepticism. We should be wary of claims that psychedelics (or any other drugs, for that matter) are “wonder drugs.” Consider methamphetamine.²⁴¹ Meth was originally hyped as a “wonder drug.” It was useful to the military for fending off fatigue and sleepiness while also generating strong feelings of alertness, vigilance, stamina, peripheral vision, and self-confidence. For civilians, meth was initially seen as valuable for working, studying, or weight loss.²⁴² Now we realize that methamphetamine, like heroin—which was also initially hyped but later crashed and burned—is a drug that, like Icarus, flew too close to the sun. The long-term use of meth leads to physical and mental deterioration, rendering “speed freaks” akin to the hungry ghosts in Buddhist cosmology: creatures always searching for satisfaction but never finding it. We do not want to make a mistake today that ruins the lives of numerous others.²⁴³ To be sure, that concern does not

require us to abandon research into psychedelics' safety, effectiveness, and uniformity; not at all. But it does militate caution lest our eagerness to find a new treatment lead us into mistakenly concluding that psychedelics work when they don't or that there are no long-term risks from their frequent, if not daily, use.

We should be skeptical of media stories about high-profile individuals who claim to have benefitted from psychedelics,²⁴⁴ sometimes by “micro-dosing”—that is, the use of minute quantities of psychedelics below the threshold that would generate hallucinations²⁴⁵ (as opposed to “minidosing”—that is, the use of quantities just above that threshold, which generates some perceptible effect²⁴⁶). Psychedelics, they say, enhance their creativity and “get the juices flowing” in fields where competition is fierce.²⁴⁷ Whether or not those stories are true—they might just be attempts (by the individuals themselves or their publicists) to make someone look like an outlaw or “edgy”—they are not the stuff that proves a drug is safe and effective. “From a scientific perspective it makes no difference how many people make such claims.”²⁴⁸ Such reports are only “anecdotal evidence, which is much like gossip; it spreads quickly, but it often unreliable.”²⁴⁹ Increasing the number of celebrities who endorse psychedelics or the amount of media attention they receive does not increase the value of what they say. Whatever their number might be, celebrity endorsements are not remotely the type of proof that the FDA demands.²⁵⁰

It should go without saying that we should be wary of claims made by people who are not treating patients but who can benefit financially from the government's approval. Cannabis advocates had considerable success persuading states to change their laws to allow cannabis to be sold for medical or recreational purposes. Private investors are attempting to repeat that outcome in the case of psychedelics.²⁵¹ Yet people who have their own financial interests in mind rather than the health of their employees or the public might not be the most impartial experts to look to for advice.²⁵²

The effort to legalize therapeutic psychedelic use is uncomfortably familiar to the one that we saw in the 1990s (and have seen since then) for legalizing medical-use cannabis.²⁵³ That opinion is not mine alone. As Professor Madras noted in 2022, “The momentum to also legalize hallucinogens shares strategies in common with movements that were calculated to increase legal access to prescription opioids and marijuana in the United States.”²⁵⁴ NIDA Director Volkow made the same point in 2023, writing in the *Journal of the American Medical Association Psychiatry* that “[d]espite the promising early results, it is clear that psychedelics are not wonder drugs, but the hype has gotten ahead of the science.”²⁵⁵

She also directly drew a parallel to the efforts to legalize cannabis for medical use: “This is reminiscent of what happened with medical cannabis: regulations pertaining to its medical use were approved, promoting a booming cannabis industry, despite lack of scientific evidence for its therapeutic efficacy.”²⁵⁶

The cannabis-legalization movement began in 1996 when California passed the Compassionate Use Act by voter referendum, ostensibly for the limited purpose of alleviating the suffering of people who were dying and in chronic pain.²⁵⁷ Yet the available evidence—some of which came from the mouths of the act’s own supporters²⁵⁸—justifies the inference that the 1996 California law was a sham to allow for recreational use.²⁵⁹ The same can be said of the medical-use programs in other states.²⁶⁰ The states that legalized cannabis did not await an FDA determination that botanical cannabis is safe, effective, and uniformly made, nor did the states conduct their own investigations and make those findings themselves. Perhaps acting out of the mistaken belief that compassion for the suffering or dying can substitute for sound medical judgment, perhaps to find a new resource stream to fund existing or new projects, perhaps to satisfy constituents who wanted to use cannabis for medical or recreational purposes, perhaps to trade off (“log-roll”) a vote for legalization in return for a vote in favor of a different bill—whatever the reason might have been, state legislators presumed to enjoy the medical knowledge or wisdom to reject the federal government’s long-standing decision that agricultural cannabis has not been proved to be a safe, effective, and uniform drug.²⁶¹

We face the same risk. The same strategies that were used effectively to legalize cannabis for medical use are now being retooled for psychedelics.²⁶² “One such strategy is to minimize potential adverse consequences and dismiss evidence-based safety concerns for general use.”²⁶³ Another strategy is to “recruit mainstream media to enthusiastically endorse a class of drugs and shape restricted access as a political ‘war on drugs’ (rather than acknowledge the need to exercise caution),” as well as to “develop industry-led campaigns to increase demand, and advocate legalization as a source of tax revenue.”²⁶⁴ Then there is the always popular strategy of using celebrities to tout a product, including psychedelics.²⁶⁵ One way or another, parties who hope to make millions from the sale of psychedelics will attempt to find a way to persuade legislatures to permit their retail sale.²⁶⁶

The Problem of Drug-Impaired Driving. At the risk of being tedious,²⁶⁷ it behooves me to note that legalizing psychedelics, even just for therapeutic use, will aggravate the problem that we already face from drug-impaired drivers. As the FDA explained in its 2023 guidance

document, “[p]sychedelic drugs can cause intense perceptual disturbances and alterations in consciousness that can last for several hours.”²⁶⁸ While undergoing a psychedelic treatment, users can mistakenly judge physical dimensions and time, and some psychedelics can impair a person’s motor coordination and working memory.²⁶⁹ That might be a manageable issue when treatment is administered in a controlled, comfortable setting with a qualified professional available to remind a patient that his or her perceptions are not real,²⁷⁰ but it is not exactly a state of mind conducive to safe vehicle handling on the nation’s roadways.²⁷¹ Consider the words of Timothy Leary: “For the unprepared, the heavy game players, those who anxiously cling to their egos, and for those who take the drug in a non-supporting setting, the struggle to regain reality begins early and usually lasts to the end of their session.”²⁷² Well, he would know. A person undergoing such an experience has no business driving a motor vehicle.

The FDA has recognized that psychedelics use can impair one’s driving skills, explaining when it announced the approval of the ketamine isomer called Spravato that it “may impair attention, judgment, thinking, reaction speed and motor skills,” so “[p]atients should not drive or operate machinery until the next day after a restful sleep.”²⁷³ The U.S. National Highway Traffic Safety Administration (NHTSA) agrees. In a 2014 report, the NHTSA wrote that while LSD can have person-specific effects and while “the incidence of LSD in driving under the influence cases is extremely rare”—it likely occurs far less often than alcohol-impaired or cannabis-impaired driving²⁷⁴—the psychological effects of LSD include “[h]allucinations, increased color perception, altered mental state, thought disorders, temporary psychosis, delusions, body image changes, and impaired depth, time and space perceptions.”²⁷⁵ Users can feel several different emotions simultaneously or rapidly swing back and forth from one to another.²⁷⁶ And that’s when a user is *enjoying* his or her experience. “‘Bad trips’ may consist of severe, terrifying thoughts and feelings, fear of losing control, and despair.”²⁷⁷ No one driving on a freeway wants to be mistaken for a White Rabbit by someone behind the wheel who’s tripping. In sum, legalizing psychedelic use will increase the number of drivers who should not be behind the wheel, which in turn will increase the number of roadway crashes, serious injuries, and fatalities.

Yet few people who have discussed this research development—including the physicians and researchers who have published many of the articles supporting psychedelic therapy—have addressed the problem of driving under the influence of those drugs.²⁷⁸ That is disappointing and distressing. It is not as if this concern is brand new. After all, physicians advise patients not to drive for 24 hours (or more) after general anesthesia because

it impairs cognitive and psychomotor functions necessary for safe vehicle handling.²⁷⁹ That is why physicians want their patients to be driven home by a responsible third party after receiving general anesthesia.

The commentators who have addressed the highway safety problems posed by psychedelic use have recognized that no one should drive a motor vehicle while under the influence of any psychoactive drug, including psychedelics.²⁸⁰ As several researchers have explained, “[t]he perceptual and psychomotor distortions associated with hallucinogen use have alarming implications for driving safety,” such as “impairment in attention, focus, memory, response time, motor abilities, and the interpretation of visual and auditory stimuli.”²⁸¹ Atop that, “[d]riving under the influence of hallucinogens is also associated with risk-taking and impulsive behaviors such as speeding or disregarding traffic signals,” as seen in “increased collisions” in “experimental groups.”²⁸² What is more, police officers can use Breathalyzers to measure a driver’s blood-alcohol content to learn whether he or she is over the legal limit of grams per deciliter (g/dL),²⁸³ but there is no similar roadside test yet available that an officer can use to determine whether someone is under the influence of a psychedelic. Legalizing psychedelics atop the legalization of cannabis is likely to offset the remarkable success that society has had over the past four decades in reducing the number of alcohol-induced traffic crashes, injuries, and fatalities. The result could be a step backwards in public safety.²⁸⁴

There is a response to that argument, and it would go like this: “Fine. Driving under the influence of psychedelics is unlawful and risks injury or death to others. And, yes, that is why ambulatory patients are told not to drive for a full day after receiving general anesthesia. But that analogy needs to be played out in full. An estimated 21 million people receive general anesthesia each year for surgery,²⁸⁵ and ambulatory patients are released to the care of a third party with the injunction not to drive for 24 hours. Society should be free to rely on the same admonition for patients who have received not a general anesthetic, but a psychedelic. After all, there is no good reason to deny people safe, effective, and available relief from afflictions like depression just because a small number of users will violate the rule against driving after use.”

That response is a reasonable one, but it is not a slam dunk.

For many patients, surgery is the only route to enable them to save their lives or return them to a better state of health. Tumors do not remove themselves, and broken or damaged limbs and joints might need to be reset or replaced. Perhaps the same concern would justify psychedelic treatment for someone who is potentially suicidal or is so debilitated by a disorder

that truly no other treatment can offer any relief from an utterly miserable existence. But a problem lies in distinguishing those patients from the ones who can fake their way to receive psychedelics or who find physicians willing to look the other way when a patient makes his or her case. Patients cannot fake x-rays or blood tests, but the average thespian might be able to portray someone claiming to be severely depressed via a telemedicine video-call with a physician.²⁸⁶

We know that psychedelics have been used for medical purposes but without onsite medical supervision, as well as recreationally.²⁸⁷ Just as some people have used a host of other illicit drugs for recreational purposes, some individuals will be highly motivated to find someone willing to prescribe psychedelics for that use. Though we might wish it were not so, there is no rule of life or law guaranteeing that every physician will be noble.²⁸⁸ State legislatures are entirely justified in taking that fact into account and should not be condemned if they conclude that the risk of driving while tripping is too great to force upon potential innocent victims.²⁸⁹

Some primitive cultures (and some contemporary ones as well) treat hallucinogens reverentially “as being sacred, put on the earth by the Supreme being(s) to allow communion between the spirit and the material worlds for the purposes of healing and divination.”²⁹⁰ Those cultures disallow the use of hallucinogens for “recreational or frivolous purposes” or beyond a “strict ritual context.”²⁹¹ By contrast, there are no voluntarily followed or socially enforceable cultural guidelines that prevent tripping for fun and profit in the United States. “[C]ontemporary use of hallucinogens often distorts ancient traditions, compromises inherent safeguards, and sets the stage for dangerous abuse.”²⁹² In some quarters, it takes little coaxing to generate widespread drug use. As a result, “[w]hat once was a sacred and reverent utilization of psychedelic substances among tribal peoples has devolved into the profaned and pathological phenomenon we now define as drug abuse.”²⁹³

As far as the FDA’s responsibility goes, the risk that approval of psychedelics would increase the number of drug-impaired drivers is not a ground for disapproval of an otherwise beneficial drug. Opioids have that effect too. But the FDA could require a warning label about the risks of driving or operating other types of potentially dangerous machinery after consuming a psychedelic. The FDA or another branch of the federal government—such as the Department of Health and Human Services or the White House Office of National Drug Control Policy (ONDCP)—could issue an official advisory to drug manufacturers, physicians, and the public about the dangers of driving under the influence of a prescribed psychedelic. During the

Obama Administration, ONDCP found that the problem of drug-impaired driving was as serious as the parallel problem of alcohol-impaired driving and demands an “equivalent” response.²⁹⁴ That response is particularly necessary given the number of states that now have medical-use or recreational-use cannabis programs.

Cannabis-impaired driving is becoming an even greater public health problem than it was in 2010. Sadly, neither the Obama, Trump, nor Biden Administration has followed through on ONDCP’s conclusion. None of those Presidents treated drug-impaired driving as a serious problem; none ordered federal officials to combat drug-impaired driving; and none used the bully pulpit to educate the public. Were the FDA to approve psychedelics for medical use, the agency would have the opportunity to address those shortfalls by confirming its importance, by urging ONDCP to coordinate a federal response, and by encouraging Congress to help the states and localities addressing this problem.²⁹⁵

Conclusion

Depression causes its sufferers intense, all-encompassing, and unrelenting psychological misery, which is why MDD is strongly associated with suicide. PTSD forces some trauma victims, such as servicemembers, to relive a painful or frightening experience as if it were happening again and again. Substance abuse disorders shackle users to a life devoted to reliving a fleeting euphoria or avoiding a deep abyss. Psychedelics hold promise for people who suffer from those disorders, as well as others. Science certainly should continue its recently reinvigorated investigation of the potential benefits of this category of drugs.

But we must be sure not to let our desire to learn whether psychedelics truly are therapeutic, and at a cost that society is willing to bear, blind us to what the results of those inquiries reveal or don’t yet tell us. Wishing on a star might work in songs and movies, but it doesn’t make dreams come true in real life. Here, as elsewhere, we should remember that there might have been eminently sensible reasons why a particular category of drugs was outlawed. Perhaps the reason was that there was no proof (or only an inadequate amount) that those drugs, when used regularly on a long-term basis, would not cause long-term injury to patients. Perhaps it was a reluctance to force patients or innocent third parties to bear the cost of our mistaken judgment as to the safety and efficacy of drugs like psychedelics. Those reasons or others might still have currency today despite the hosannahs we hear from some advocates about psychedelics.

Author Michael Pollan expressed the opposing viewpoints in 2018 better than I can today:

We shouldn't forget that irrational exuberance has afflicted psychedelic research since the beginning, and the belief that these molecules are a panacea for whatever ails us is at least as old as Timothy Leary. It could well be that the current enthusiasm will eventually give way to a more modest assessment of their potential. New treatments always look shiniest and most promising at the beginning. In early studies and with small samples, the researchers, who are usually biased in favor of finding an effect, have the luxury of selecting the volunteers most likely to respond. Because their number is so small, these volunteers benefit from the care and attention of exceptionally well-trained and dedicated therapists, who are also biased in favor of success. Also, the placebo effect is usually strongest in a new medication and tends to fade over time, as observed in the case of antidepressants; they don't work nearly as well today as they did upon their introduction in the 1980s. None of these psychedelic therapies have yet proven themselves to work in large populations; what successes have been reported should be taken as promising signals standing out from the noise of data, rather than as definitive proofs of cure.

Yet the fact that psychedelics have produced such a signal across a range of indications can be interpreted in a more positive light. When a single remedy is prescribed for a great many illnesses, to paraphrase Chekhov, it could mean those illnesses are more alike than we're accustomed to think. If a therapy contains an implicit theory of the disorder it purports to remedy, what might the fact that psychedelic therapy seems to address so many indications have to tell us about what those disorders might have in common? And about mental illness in general?²⁹⁶

The FDA will now address those questions when it decides how to classify the drug MDMA in light of the new evidence of its utility. That is the approach we should have followed in the case of cannabis but didn't. Well, better late than never. We can't undo past mistakes, but we can refuse to treat them as binding precedents. Whatever the FDA's decision might be, at least this time we have the right agency making the call.

Endnotes

1. “LSD and other psychedelics may be defined as amplifiers or activators of mental processes. Leading to heightened awareness of perceptions, thoughts, and feelings, as well as loosening of psychological defenses. This may reveal aspects of mind normally out of awareness and catalyze experiences that are powerfully novel and galvanizing. The complex effects of psychedelics have resulted in a variety of terms applied to describe them: *psychotomimetic* (mimicking the symptoms of psychosis), *hallucinogen* (generating hallucinations), *entheogen* (generating experiences of the divine), and *psychedelic* (mind revealing).” Kristine Panik & David E. Presti, *LSD*, in *HANDBOOK OF MEDICAL HALLUCINOGENS* 159, 159 (Charles S. Grob & Jim Grigsby eds., 2021); see also LESTER GRINSPOON & JAMES B. BAKALAR, *PSYCHEDELIC DRUGS RECONSIDERED* 9 (1997) (“A psychedelic drug is one which, without causing addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis.”); Peter Grinspoon, *Back to the Future: Psychedelic Drugs in Psychiatry*, HARV. HEALTH PUBL’G BLOG, June 22, 2021, <https://www.health.harvard.edu/blog/back-to-the-future-psychedelic-drugs-in-psychiatry-202106222508> (“Psychedelic drugs are a loosely grouped class of drugs that are able to induce altered thoughts and sensory perceptions. At high doses some of them, such as LSD, can cause visual hallucinations. Many people have heard of ‘magic mushrooms’ which contain the active ingredient psilocybin. Psilocybin can also alter perceptions and cause hallucinations at high doses. Other drugs, such as ecstasy, primarily affect one’s mood and sensation of closeness with others. Still others, such as ketamine, have traditionally been used as anesthetics, but also act as hallucinogens and can cause dreamlike states. Ayahuasca, which is found in the jungles of South America, has been used by traditional cultures for centuries. While these drugs and medicines are loosely described under a general rubric, there are big differences between them.”).
2. See, e.g., ALDOUS HUXLEY, *THE DOORS OF PERCEPTION* (1954); TIMOTHY LEARY ET AL., *THE PSYCHEDELIC EXPERIENCE* (Reprint 2022) (1964) [hereafter LEARY ET AL. *PSYCHEDELIC EXPERIENCE*]; HUNTER S. THOMPSON, *FEAR AND LOATHING IN LAS VEGAS* (1998) (1971); TOM WOLFE, *THE ELECTRIC KOOL-AID ACID TEST* (1968) (an account of Kesey and his friends, the Merry Pranksters).
3. James J.H. Rucker et al., *Psychiatry and the Psychedelic Drugs: Past, Present, and Future*, 148 *NEUROPHARMACOLOGY* 200, 201 (2018). “Timothy Leary, charismatic ringmaster of the Harvard group”—who, along with his co-authors Ralph Metzner and Richard Alpert, “attained legendary status in the intervening decades”—“was soon to become the pied piper of the acid generation—using the media as a pulpit to proclaim his dicey message of ‘tune in, turn on, drop out’—before he fell into disgrace and disrepute.” Daniel Pinchbeck, *Introduction* (2007), in LEARY ET AL. *PSYCHEDELIC EXPERIENCE*, *supra* note 2, at ix. For a description of the potential effects, see GRINSPOON & BAKALAR, *supra* note 1, at 89–90 (citation omitted): “The array of psychedelic experiences is vast almost beyond belief.... The time, the place, the companions, intelligence, imagination, personality, emotional state, and cultural background of the user can be decisive. As small a matter as opening or closing the eyes, changing the music, or slightly increasing the dose can transform the quality of the experience. In experiments, most drugs make all the subjects feel more alike; LSD actually tends to accentuate any differences in mood that exist among subjects at the start.... The narratives of psychedelic trips are as luxuriant and varied as myths, dreams and psychoanalytic revelations. In a sense, there is no ‘psychedelic effect’ or ‘psychedelic state’; to say that someone has taken LSD tells little more about the content and import of his experience than to say that he has had a dream.”
4. “[I]t was partly the way some adults flattered them as spiritual and social innovators that made young drug users so confident of their judgment. Some professional people—sociologists, psychologists, journalists, clergymen—were so excited by the hippies’ proclamations of messianic transcendence and social revolution that they abandoned their own judgment and invested disappointed hopes for drastic and immediate change in a movement that made promises far beyond its ability to deliver.” GRINSPOON & BAKALAR, *supra* note 1, at 75.
5. The Beatles, *Lucy in the Sky with Diamonds*, on *Sgt. Pepper’s Lonely Hearts Club Band* (1967).
6. The Beatles, *Tomorrow Never Knows*, on *Revolver* (1966). John Lennon took the song’s line “Turn off your mind, relax, and float downstream” from the Leary, Metzner, and Alpert book *The Psychedelic Experience*. Pinchbeck, *supra*, in LEARY ET AL. *PSYCHEDELIC EXPERIENCE*, *supra* note 2, at xiv; *id.* at 6.
7. The Beatles, *I Am the Walrus*, on *Magical Mystery Tour* (1967).
8. Jefferson Airplane, *White Rabbit*, on *Surrealistic Pillow* (1967).
9. The Doors, *Break on Through (To the Other Side)*, on *The Doors* (1967). The band took its name from the title to Aldous Huxley’s book *The Doors of Perception*.
10. The Grateful Dead, *Black Peter*, on *Workingman’s Dead* (1970).
11. *Easy Rider* (Columbia Pictures 1969).
12. *Yellow Submarine* (Apple Films 1968).
13. Pinchbeck, *supra*, in LEARY ET AL. *PSYCHEDELIC EXPERIENCE*, *supra* note 2, at ix.
14. GRINSPOON & BAKALAR, *supra* note 1, at 70–71.
15. See Grob & Grigsby, *supra* note 1, at xi; GRINSPOON & BAKALAR, *supra* note 1, at 38–55; HALLUCINOGENS AND SHAMANISM (Michael J. Hamer ed., 1973); Mason Marks & I. Glenn Cohen, *Psychedelic Therapy—A Roadmap for Wider Acceptance and Utilization*, 27 *NATURE MED.* 1669, 1670 (2021). Psychedelics are still used for that purpose in some religions today. See, e.g., *Gonzales v. O Centro Espirita Beneficente Uniã do Vegeta*, 546 U.S. 418 (2006); *Employment Div., Oregon Dep’t of Human Resources v. Smith*, 494 U.S. 872 (1990). Religions that use hallucinogens do not do so profligately and rely on social and cultural guideposts for their use. See Matthew W. Johnson et al., *Human Hallucinogen Research: Guidelines for Safety*, 22 *J. PSYCHOPHARMACOLOGY* 613,

- 613 (2008) (“Hallucinogens have been used by indigenous cultures for millennia.... These cultures have restricted hallucinogen use to sacramental and healing contexts, with these two often being inseparably intertwined. Remarkably, apparently without exception, such cultures view hallucinogenic plants and fungi as being of divine origin.... Given this orientation, it is not surprising that their ingestion is often tightly restricted, with use controlled by ceremonial guidelines including taboos against improper use.... Indigenous cultures restrict use of hallucinogens to highly ritualized, sacred ceremonies such as those designed to serve as rites of passage, or to set the occasion for divination and spiritual or physical healing.”) (citations omitted).
16. See, e.g., Rucker et al., *supra* note 3, at 201–04. For example, “[t]he investigation of alcoholism treatment in the early 1950s operated from a hypothesis that a psychedelic-induced state of somatic and cognitive chaos might have similarities to the life-threatening delirium tremens (DTs) of alcohol withdrawal, and foster such a psychic shake-up that sobriety would be a result.” Panik & Presti, *supra*, in Grob & Grigsby, *supra* note 1, at 167.
 17. See, e.g., Rucker et al., *supra* note 3, at 201–04.
 18. GRINSPOON & BAKALAR, *supra* note 1, at 75.
 19. *Id.* at 85.
 20. See MOHEB COSTANDI, NEUROPLASTICITY (2016); Grinspoon, *supra* note 1 (“According to Dr. Jerrold Rosenbaum, the director of the newly created Center for the Neuroscience of Psychedelics at Massachusetts General Hospital and former psychiatrist-in-chief at MGH, the short answer is, ‘Psychedelics induce the brain to change transiently in ways that appear to allow a reset to take place and permit alterations in previously “stuck” ways of feeling and thinking about things.’ There are likely several ways in which psychedelics can accomplish this: new connections are briefly made in neural networks while the resting state of the brain (or the ‘default mode network’) loses connectivity—then it restores itself. ‘It’s like rebooting your computer.’ This is how stuck patterns of thinking are thought to shift. Also, new connections between neurons are formed, a process that is called neuroplasticity. Finally, the psychedelic drugs themselves can put patients into a transient state where they can better process memories, feelings, and past trauma, and can ‘reemerge with a new perspective on them that is freeing and healing’—also called psychedelic-assisted therapy.”).
 21. “The thoughts and memories of depressed people run along rails of negativity and guilt from which they cannot escape, called ‘tramline thinking.’ This negative thinking develops a life of its own, pushing the person deeper into their depressive ruminations. [¶] You can get a sense of what this feels like from this description by Scottish philosopher Thomas Carlyle: ‘It was one huge, dead, immeasurable steam-engine, rolling on, in its dead indifference, to grind me limb from limb.’” DAVID NUTT, PSYCHEDELICS: THE REVOLUTIONARY DRUGS THAT COULD CHANGE YOUR LIFE 94 (2024).
 22. “Addiction begins as a behavior that’s enjoyable or provides relief, such as cigarettes for stress or alcohol for social anxiety or cannabis for insomnia. But eventually it becomes a self-sustaining habit. The positive memories of addictions are laid down as deep-seated memories that link the location, people involved and experience of the addiction with the positive emotional effects. [¶] Once addiction sets in, choosing to stop is very difficult, often impossible. The urge to engage in the behavior becomes so powerful that it interferes with normal life, often to the point of overtaking work, personal relationships and family activities. This quote from a patient of the physician and addiction expert Dr. Gabor Mate sums it up: ‘When I was using, I had tunnel vision.’ [¶] Anyone who’s met an addict knows that most addicts don’t want to take drugs or drink but are compelled to by something that’s beyond them” NUTT, *supra* note 21, at 147 (footnote omitted).
 23. “People with PTSD constantly reexperience their trauma and the emotions that come with it. Sufferers are easily startled and quick to anger. They might have flashbacks and intrusive memories, dark thoughts, panic attacks, nightmares and other sleep problems. They might avoid things that remind them of the trauma, and so disconnect from emotions and from friends and family. They are more likely to suffer from anxiety, depression, cognitive and memory problems and addictions, and are at high risk of suicide.” NUTT, *supra* note 21, at 170. As for factors that contribute to PTSD: “There are a number of environmental and biological risk factors that contribute to the development and maintenance of PTSD, and poor PTSD treatment outcomes are associated with several comorbid conditions that include childhood trauma, alcohol and substance use disorders, depression, suicidal ideation, and dissociation.” Jennifer M. Mitchell et al., *MDMA-Assisted Therapy for Severe PTSD: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study*, 27 NATURE MED. 1025, 1025 (2021) (footnotes omitted) [hereafter Mitchell et al., *MDMA and Severe PTSD*].
 24. Or Psychedelic-Preceded Therapy (PPT). See Guy M. Goodwin et al., *Must Psilocybin Always “Assist Psychotherapy”?*, 181 AM. J. PSYCHIATRY 20, 23 (2024).
 25. See Michael Mithoefer & Annie Mithoefer, *MDMA*, in Grob & Grigsby, *supra* note 1, at 233–63; Scott Shannon et al., *Therapeutic and Social Uses of MDMA*, in Grob & Grigsby, *supra* note 1, at 264–76.
 26. See *infra* text accompanying notes 85–88.
 27. See Tristan McClure-Begley & Bryan L. Roth, *The Promises and Perils of Psychedelic Pharmacology for Psychiatry*, 21 NATURE REVIEWS DRUG DISCOVERY 463, 470 (2022) (noting “the lack of known ‘rescue’ medications to abort unfavourable psychedelic experiences”).
 28. Charles F. Reynolds III, *Psilocybin-Assisted Supportive Psychotherapy in the Treatment of Major Depression—Quo Vadis?*, 78 JAMA PSYCHIATRY 476, 477 (2021); Rucker et al., *supra* note 3, at 201.
 29. See Stephen Ross et al., *Psilocybin*, in Grob & Grigsby, *supra* note 1, at 181–214.
 30. See Will van Derveer, *Mescaline*, in Grob & Grigsby, *supra* note 1, at 227–32; Ioanna A. Vamvakopoulou et al., *Mescaline: The Forgotten Psychedelic*, 222 NEUROPHARMACOLOGY 209294, at 1 (2023) (“[T]he use of classical psychedelics has been proposed to be effective in a variety of psychiatric disorders such as alcoholism, depression, post-traumatic stress disorder, and obsessive-compulsive disorder....”) (citations omitted).
 31. See Draulio Barros de Araujo et al., *Biological and Psychological Mechanisms Underlying the Therapeutic Use of Ayahuasca*, in Grob & Grigsby, *supra* note 1, at 277–93.

32. See Kenneth Alper, *The Ibogaine Project*, in Grob & Grigsby, *supra* note 1, at 294–312. Ayahuasca is under investigation as a treatment for depression and traumatic brain injury (TBI). Kirsten N. Cherian et al., *Magnesium–Ibogaine Therapy in Veterans with Traumatic Brain Injuries*, *NATURE MEDICINE*, Nov. 10, 2023, <https://doi.org/10.1038/s41591-023-02705-w>; Grob & Grigsby, *supra* note 1, at xii. Perhaps ibogaine can help people suffering from addiction, but it's not likely to generate much use as a recreational drug. See *Kentucky Eyes Ibogaine, a Psychedelic, to Treat Opioid Addiction*, *ECONOMIST*, Dec. 30, 2023, <https://www.economist.com/united-states/2023/12/30/kentucky-eyes-ibogaine-a-psychedelic-to-treat-opioid-addiction>, (“Ibogaine is not your college dorm-room type of psychedelic. The drug comes from the iboga plant, a Central African shrub, and it has been used in tribal coming-of-age rituals. It causes trips so unpleasant that even the most adventurous drug-users shy away from a second dose. Along with mystical experiences and feelings of spiritual transformation, ibogaine can cause pain, anxiety, sweating, nausea and irregular heart rhythms. Some have died from cardiac events. The experience can last up to two days, with several days of rest needed after. It can be an extremely difficult experience, says Andrew Tatarsky, a psychologist at the Freedom Institute, an outpatient treatment centre in New York City. ‘It’s not something you want to take for fun or party with.’”).
33. See Gary Bravo, *Ketamine*, in Grob & Grigsby, *supra* note 1, at 327–44. Technically, ketamine is a dissociative anesthetic, not a psychedelic, but is often discussed with the latter because of its psychoactive effect at subanesthetic levels. See *id.* at 327, 328, 332–33; Angela N. Phan & Garth E. Terry, *Systematic Review and Rationale of Using Psychedelics in the Treatment of Cannabis Use Disorder*, 14 *FRONTIERS IN PSYCHIATRY* 1144276, at 7 (2023). The FDA approved the drug Spravato (a form of ketamine) as a treatment for major depressive disorder, with suicidal thoughts, or treatment-resistant depression. See BITA MOGHADDAM, *KETAMINE* 121–22 (2021); Gerard Sanacora et al., *A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders*, 74 *JAMA PSYCHIATRY* 399 (2017).
34. See, e.g., José Carlos Bouso et al., *Personality, Psychopathology, Life Attitudes and Neuropsychological Performance Among Ritual Users of Ayahuasca: A Longitudinal Study*, 7 *PLoS ONE* e42421 (2012).
35. GRINSPOON & BAKALAR, *supra* note 1, at 9; see also, e.g., Mithoefer & Mithoefer, in Grob & Grigsby, *supra* note 1, at 235–36 (noting that MDMA differs from classic psychedelics like LSD and psilocybin; “MDMA rarely causes hallucinations and has less tendency to be disorienting or frightening than many psychedelics.”); Romain Nardou et al., *Psychedelics Reopen the Social Reward Learning Critical Period*, 618 *SCIENCE* 790, 791–92 (2023) (noting that “the psychotropic effects of MDMA include an altered state of consciousness shared by all psychedelics,” but adding that “MDMA is classified as an ‘empathogen’ because its acute subjective effects are distinctly prosocial in quality” and “this quality is not shared by hallucinogenic psychedelics such as psilocybin and LSD, dissociative psychedelics such as ketamine, or oneirogenic psychedelics [viz., substances that produce a dreamlike state of consciousness] such as ibogaine”) (endnotes omitted).
36. GRINSPOON & BAKALAR, *supra* note 1, at 9.
37. *Id.* at 29.
38. *Id.*
39. *Id.* at 61.
40. See *supra* notes 1 & 3.
41. Nardou et al., *supra* note 35, at 790; see also Phan & Terry, *supra* note 33, at 7 (“Psychedelic compounds can contribute to lasting effects in an individual within psychological domains such as mystical experience, mood and affect, and personality. Lasting behavior change can be triggered by an experience that is vivid, benevolent, mystical, and/or characterized by important insights. These ‘mystical experiences’ are thought to provide profound alterations in perception along with a sense of meaningfulness, insightfulness, and unity. This state, achieved with support of psychedelics, is thought to be more malleable, flexible, sensitive to the environment, and open to change. Such experiences have also been reported with non-classic psychedelics, including ‘dissociative’ compounds [viz., compounds that produce feelings of dissociation from the self or surrounding environment] such as ketamine, or the ‘entactogen’ [viz., empathy-arousing or sympathy-arousing] MDMA. The therapeutic effects from these experiences can be enduring, and it is conceptualized that during the psychedelic experience a therapeutic window in the mind is temporarily opened which facilitates gained insight and emotional release. In conjunction with psychotherapeutic support, this insight can potentially lead to a healthy revision of outlook and lifestyle.”) (endnote omitted).
42. LEARY ET AL. PSYCHEDELIC EXPERIENCE, *supra* note 2, at 3.
43. *Id.* Leary used the Tibetan model of the *bardo*—the evanescent period between life and rebirth or nirvana—to describe “three phases” of a psychedelic experience. “The first period (*Chikhai Bardo*) is that of complete transcendence—beyond words, beyond space-time, beyond self. There are no visions, no sense of self, no thoughts There are only pure awareness and ecstatic freedom from all games and biological involvements.” *Id.* at 4–5 (footnote omitted). (Interestingly, Leary defined “games” as “behavioral sequences defined by roles, rules, rituals, goals, strategies values, language, characteristic space time locations and characteristic patterns of movement,” *id.* at 5 n.*—which is everything that makes civilization possible or distinguishes reality from dreams.) “The second lengthy period involves self, or external game reality (*Chonyid Bardo*)—in sharp exquisite clarity or in the form of hallucinations (karmic apparitions). The final period (*Sidpa Bardo*) involves the return to routine game reality and the self.” *Id.* at 5. Traversing “the psychedelic experience is fluid and ever-changing,” and “[t]ypically the subject’s consciousness flicks in and out of these three levels with rapid oscillations.” *Id.*
44. See *supra* note 20 and accompanying text. Nonetheless, there is more to learn. For example, we know that psychedelics bond with neural receptors in the frontal cortex, the serotonin or 5-hydroxytryptamine (5-HT) family of receptors, particularly the 5-HT_{2A} subtype. CNTR. FOR DRUG EVALUATION AND RESEARCH (CDER), U.S. FOOD & DRUG ADMIN., *PSYCHEDELIC DRUGS—CONSIDERATIONS FOR CLINICAL INVESTIGATIONS, DRAFT GUIDANCE FOR INDUSTRY* (June 2023); TORSTEN PASSIE, *THE SCIENCE OF MICRODOSING PSYCHEDELICS* 154 (2019); Natasha Loder, *Psychedelic Medicines Are Expanding into the Public Consciousness*, *ECONOMIST*,

- Nov. 18, 2022, <https://www.economist.com/the-world-ahead/2022/11/18/psychedelic-medicines-are-expanding-into-the-public-consciousness>; Ross et al., in Grob & Grigsby, *supra* note 29, at 185. The 5-HT system modulates or fine-tunes the effects of other neurotransmitter systems and their behavioral effect. PASSIE, *supra*, at 154. Because there seems to be no specific action for which the 5-HT system is responsible, the system is said to be “involved everywhere, but responsible for nothing.” *Id.* There is experimental evidence that 5-HT is involved in mood regulation, but precisely how is “still [circa 2019] virtually unknown.” *Id.* Another unknown factor is whether—and, if so, how—LSD activates “second and third messenger systems” that, once set in motion, generate “a further chain of [cellular] reactions.” *Id.* at 133, 135, 154–61. One recent scholar theorized that psychedelics can turn off the brain’s default mode network—viz., “the very highest level of the brain and the overarching conductor of global brain function—to reset its network of connections. NUTT, *supra* note 21, at 76–80.
45. Myron J. Stolaroff, *Using Psychedelics Wisely*, in HALLUCINOGENS: A READER 100 (Charles S. Grob ed., 2002) (“The great value in these chemicals is that, in some way still not scientifically explained, they dissolve the boundaries to the unconscious mind. They give us access to our repressed and forgotten material, to the Shadow that C.G. Jung so effectively dealt with, to the archetypes of humanity, to an enormous range of levels of thought, and to the wellspring of creativity and mystical experience that Jung called the creative unconscious.”).
 46. *Id.*
 47. James C. Harris, *Psychedelic-Assisted Psychotherapy and Carl Jung’s Red Book*, 78 JAMA PSYCHIATRY 815, 815 (2021).
 48. See, e.g., Matthew W. Johnson et al., *The Abuse of Medical Psilocybin According to the 8 Factors of the Controlled Substances Act*, 142 NEUROPHARMACOLOGY 143, 144 (2018) (“The benefits of psilocybin in the treatment of depression, anxiety and other disorders were first suggested in the 1960s when psilocybin was marketed in many countries, including the United States (US) under the trade name Indocycin® by the Swiss pharmaceutical company, Sandoz. Indocycin® provided a shorter acting alternative to lysergic acid diethylamide (LSD) which has a similar primary pharmacological mechanism of action, now known to be agonist or partial agonist effects at the 5-HT_{2A} receptor.... While Indocycin® was used safely as an adjunct to psychotherapy, eventually the societal backlash in the US and other countries in the 1960s...led to a ban on marketing and possession of ‘hallucinogenic’ drugs in the US in 1965, and led Sandoz to discontinue manufacturing and marketing of Indocycin® in 1966....”) (citations omitted); see *infra* note 60.
 49. GRINSPORN & BAKALAR, *supra* note 1, at 244–53; McClure-Begley & Roth, *supra* note 27, at 463; Rucker et al., *supra* note 3, at 201.
 50. GRINSPORN & BAKALAR, *supra* note 1, at 193.
 51. *Id.* at 194.
 52. “Between 1950 and the mid-1960s there were more than a thousand clinical papers discussing 40,000 patients, several dozen books, and six international conferences on psychedelic drug therapy. It aroused the interest of many psychiatrists who were in no sense cultural rebels or especially radical in their attitudes.” *Id.* at 192; see also, e.g., Charles S. Grob et al., *Pilot Study of Psilocybin Treatment for Anxiety in Patients with Advanced-Stage Cancer*, 68 ARCHIVES GEN'L PSYCHIATRY 71, 71 (2011) (“From the late 1950s to the early 1970s, research was carried out exploring the use of hallucinogens to treat the existential anxiety, despair, and isolation often associated with advanced-stage cancer.”) (endnotes omitted); Sean J. Belouin & Jack E. Henningfield, *Psychedelics: Where We Are Now, Why We Got Here, What We Must Do*, 142 NEUROPHARMACOLOGY 7, 8–9 (2018) (“[LSD] was heralded in the medical literature and popular press with great promise for the treatment of a variety of serious mental health disorders including anxiety, depression, schizophrenia, war time stress reactions, alcoholism and other substance use disorders.... Its clinically documented favorable safety profile, potency, and its ability to produce powerful and occasionally enduring beneficial psychological effects, led many prominent leaders in the behavioral science field along with the pharmaceutical industry to view LSD, and possibly related chemical entities, as potential breakthroughs in many areas of mental illness, including various forms of drug addiction. [¶] The promise of LSD, psilocybin, mescaline and other psychedelic substances as tools in psychiatric investigation and their potential for medicinal application was pursued vigorously by many leading researchers in psychiatry and the emerging fields of neuropharmacology and neuropsychopharmacology[.]”) (citation omitted); Muhammad Ishrat Husain et al., *Serotonergic Psychedelics for Depression: What Do We Know About Neurobiological Mechanisms of Action?*, 10 FRONTIERS IN PSYCHIATRY 1076459, at 2 (2023), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9950579/> (“Clinical research into psychedelic treatments began in the 1950s; about 40,000 individuals had been studied by the late 1960s when concerns about their safety and their recreational use led to their classification as Schedule 1 narcotics[.]”) (endnotes omitted); David Nutt et al., *Psychedelic Psychiatry’s Brave New World*, 181 CELL 24, 24 (2020). Bear in mind that during the early 1950s, there were no approved treatments for the major mental illnesses, schizophrenia and major depression. Psychiatrists were desperate for a “magic bullet” to replace ineffective talk therapy. By 1954, the first antipsychotic (chlorpromazine) was found to be effective, but LSD research in people with schizophrenia continued despite the DRAMATIC IMPROVEMENTS SEEN WITH CHLORPROMAZINE.
 53. SEE, E.G., PAUL H. HOCH ET AL., EFFECTS OF Mescaline AND Lysergic Acid (D-LSD-25), 108 Am. J. Psychiatry 579, 584 (1952) (“Mescaline and lysergic acid are drugs that disorganize the psychic integration of a person. This disorganization is much more apparent in schizophrenics than in normals.”); Vamvakopoulou et al., *supra* note 30, at 6 (describing two 1950s studies of mescaline treatment on patients diagnosed with schizophrenia; finding that mescaline reactivated or worsened the psychotic symptoms of 21 of 25 subjects in one test and had no effect on 16 of 24 subjects in the other test).
 54. Rucker et al., *supra* note 3, at 201.
 55. *Id.*
 56. “Almost from the beginning, views toward the utility of this highly unusual treatment model were polarized. The enthusiastic belief possessed by some, that this had brought psychiatry and psychology to the threshold of an entirely new and novel paradigm, was dismissed by others as unrealistic and even messianic.” Grob & Grigsby, *supra* note 1, at ix; see also, e.g., Michael Pollan, *The New Science of Psychedelics*, WALL ST. J., May

- 3, 2018, https://www.wsj.com/articles/the-new-science-of-psychedelics-1525360091?mod=article_inline (“The value of psychedelic therapy was first recognized nearly 70 years ago, only to be forgotten when what had been a promising era of research ran headlong into a nationwide moral panic about LSD, beginning around 1965. With a powerful assist from Timothy Leary, the flamboyant Harvard psychology professor, psychedelics had escaped the laboratory, falling into the eager arms of the counterculture.... Compared with other psychoactive compounds, these powerful and mysterious molecules were regarded as safe—it’s virtually impossible to overdose on a psychedelic—and nonaddictive. Rats in a cage presented with a lever to administer drugs like cocaine and heroin will press it repeatedly, unto death. LSD? That lever they press only once.”); Rucker et al., *supra* note 3.
57. See *supra* note 48.
 58. For a persuasive discrediting of the received wisdom, see MATTHEW ORAM, *THE TRIALS OF PSYCHEDELIC THERAPY* (2018), and Wayne Hall, *Why Was Early Therapeutic Research on Psychedelic Drugs Abandoned?*, 52 *PSYCHOL. MEDICINE* 26, 26–29 (2022).
 59. “Before 1963 any clinician could undertake ‘clinical research’ on an unapproved drug without conducting a formal clinical trial or seeking approval from an ethics committee.... Clinical research on a ‘promising’ new drug usually involved giving the drug to patients, often the long-stay residents of mental hospitals, and making clinical judgments about their efficacy and safety.... Under the new FDA regulations... ‘clinical research’ required a formal Clinical Trial Notification (CTN) that included a dossier of preclinical evidence to show that the drug was safe and likely to be of therapeutic value. It also required a detailed proposal for a randomized controlled trial (RCT) to assess the drug’s safety and effectiveness in treating a defined clinical disorder.... Research on psychedelic drugs came under these new regulations because very few RCTs had been conducted to assess their safety and efficacy before 1963....” Hall, *supra* note 58, at 27–28 (citations omitted). The early trials themselves had several shortcomings. According to drug policy expert Wayne Hall, those trials were characterized by a lack of controls and rationale for the particular doses administered; the frequent absence of informed consent for treatments; and the development of adverse outcomes for some people who became much more ill, even irreversibly so. *Id.* at 27 (noting that critics of the early studies argued that “their studies were too small, poorly controlled, and their assessments of outcomes were biased”) (citations omitted).
 60. *Id.*
 61. See *id.*
 62. See, e.g., Jeffery A. Lieberman, *Back to the Future—The Therapeutic Potential of Psychedelic Drugs*, 384 *NEW ENG. J. MED.* 1460, 1460 (2021); Nutt et al., *supra* note 52, at 24; Nora D. Volkow et al., *Psychedelics as Therapeutics: Potential and Challenges*, 80 *JAMA PSYCHIATRY* 979, 979–80 (2023) (“Current psychedelics research carries the baggage of past ethical transgressions, including egregious experimentation with LSD on unwitting study ‘participants’ including individuals with disabilities and those who were incarcerated in the 1950s.”).
 63. “In 1955, [Aldous] Huxley spoke of ‘a nation’s well-fed and metaphysically starving youth reaching out for beatific visions in the only way they know’—through drugs.... The fulfillment of his prophecies began when college students yearning to free themselves from the stultifying complacency of the 1950s fell under the influence of academic and literary figures promoting psychedelic drugs as a means for the permanent transformation of consciousness.... The psychedelic movement was a kind of crisis cult within Western industrial society, formed by children of affluence and leisure who were inadequately assimilated culturally and homeless psychologically.” GRINSPOON & BAKALAR, *supra* note 1, at 63.
 64. *Id.* at 168 (“strong unpleasant feelings, panic, fear of insanity or death, thoughts of suicide”); NUTT, *supra* note 21, at 121 (“[N]early half of people who took psychedelics in the 1960s reported having had a bad trip.”).
 65. Lieberman, *supra* note 62, at 1460; Dennis J. McKenna, *Plants for the People: The Future of Psychedelic Medicine in the Age of Biomedicine*, in Grob & Grigsby, *supra* note 1, at 32 (“LSD, once escaped from the laboratory, dropped like a bomb into Western society, which was already a seething broth of rapidly accelerating social, cultural, and political ferment.”).
 66. See GRINSPOON & BAKALAR, *supra* note 1, at 185–87; Hall, *supra* note 58, at 27.
 67. In the 1950s and 1960s, the federal government tested LSD on soldiers and civilians who were never told what drug they were taking. See, e.g., *United States v. Stanley*, 483 U.S. 669, 671 (1987) (“In February 1958, James B. Stanley, a master sergeant in the Army stationed at Fort Knox, Kentucky, volunteered to participate in a program ostensibly designed to test the effectiveness of protective clothing and equipment as defenses against chemical warfare. He was released from his then-current duties and went to the Army’s Chemical Warfare Laboratories at the Aberdeen Proving Grounds in Maryland. Four times that month, Stanley was secretly administered doses of lysergic acid diethylamide (LSD), pursuant to an Army plan to study the effects of the drug on human subjects. According to his Second Amended Complaint (the allegations of which we accept for purposes of this decision), as a result of the LSD exposure, Stanley has suffered from hallucinations and periods of incoherence and memory loss, was impaired in his military performance, and would on occasion ‘awake from sleep at night and, without reason, violently beat his wife and children, later being unable to recall the entire incident.’ App. 5. He was discharged from the Army in 1969. One year later, his marriage dissolved because of the personality changes wrought by the LSD.”); *Sims v. CIA*, 642 F.2d 562, 563–64 (D.C. Cir 1980) (“Between 1953 and 1966 the CIA sponsored extensive research concerning chemical, biological, and radiological materials capable of employment in clandestine operations to control human behavior. Code-named MKULTRA, the CIA’s research program included 149 subprojects undertaken on a contract basis. CIA records document the participation of at least 80 institutions and 185 researchers. Because the CIA funded MKULTRA largely through a front organization, many of the participating individuals and institutions apparently had no knowledge of their involvement with the Agency. [¶] On the basis of available documents, it appears that the CIA originally conceived MKULTRA as a defensive response to possible use by the Soviets and the Chinese of chemical and biological agents as instruments of interrogation and brainwashing. Later, however, the Agency expanded the scope of the program to include efforts to develop chemical and biological agents for use by the CIA. At least some of the subprojects tested chemical and biological substances by administering them

- to human subjects. Some of the subjects volunteered for their experimental role. Others were unwitting participants, who may never have known what happened to them. At least two persons died as the result of MKULTRA experiments. The extent of possible damage to the health of others remains unknown, because CIA records fail to disclose the identities of all experimental subjects.”) (footnotes and punctuation omitted), *appeal after remand*, 709 F.2d 45 (D.C. Cir. 1983), *aff’d in part and rev’d in part on other grounds*, CIA v. Sims, 471 U.S. 159, 161–62 & n.2 (1985); GRINSPOON & BAKALAR, *supra* note 1, at 171–72 (describing a person in the MKULTRA experiments who jumped from the third floor and died); STEPHEN KINZER, POISONER IN CHIEF: SIDNEY GOTTLIEB AND THE CIA SEARCH FOR MIND CONTROL (2019); MARTIN A. LEE & BRUCE SHLAIN, ACID DREAMS: THE COMPLETE SOCIAL HISTORY OF LSD: THE CIA, THE SIXTIES, AND BEYOND (Rev. ed. 2007); NUTT, *supra* note 21, at 117–18; Volkow et al., *supra* note 62, at 979–80 (“Current psychedelics research carries the baggage of past ethical transgressions, including egregious experimentation with LSD on unwitting study ‘participants’ including individuals with disabilities and those who were incarcerated in the 1950s.”).
68. The CSA was Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, Pub. L. No. 91-513, 84 Stat. 1242 (codified as amended at 21 U.S.C. §§ 801–904 (2018)). A “controlled substance” is “a drug or other substance, or immediate precursor, included in Schedule I, II, III, IV, or V of part B of this title,” except for “distilled spirits, wine, malt beverages, or tobacco, as those terms are defined or used in subtitle E of the Internal Revenue Code of 1954.” 21 U.S.C. § 802(6) (2018). The CSA incorporates the definition of a “drug” from the Federal Food, Drug, and Cosmetic Act and assigns drugs to one of five schedules according to their potential benefits and risks. 21 U.S.C. §§ 201(g)(1), 812, 841 (2018). The CSA and its implementing regulations govern the lawful manufacture, transportation, and distribution of controlled substances. See, e.g., 21 U.S.C. §§ 802(10), (11), (21) & (22), 822–823, 828, 829a, 831 (2018); 21 C.F.R. §§ 1306.01–1306.27 (2022). Category I is reserved for drugs, such as heroin, that lack a legitimate therapeutic use and pose a serious risk of abuse; psychedelics also wound up in that group. Lieberman, *supra* note 62, at 1460; Nutt et al., *supra* note 52, at 24 (“[O]nce LSD became used recreationally by young people, it was banned, and most other psychedelics were sucked into the legislation; research on their potential therapeutic efficacy ground to a halt.”).
 69. See 21 U.S.C. §§ 812, 841 (2018); 21 C.F.R. §§ 1308.01, 1308.11 (2023).
 70. Though illegal, psychedelics can be found in the underground economy. See, e.g., SUBSTANCE ABUSE & MENTAL HEALTH SERVS. ADMIN., KEY SUBSTANCE USE AND MENTAL HEALTH INDICATORS IN THE UNITED STATES: RESULTS FROM THE 2021 NATIONAL SURVEY ON DRUG USE AND HEALTH 18 (2022), (“In 2021, 2.6 percent of people aged 12 or older (or 7.4 million people) used hallucinogens in the past year (Figures 14 and 19 and Table A.7B). The percentage was highest among young adults aged 18 to 25 (7.1 percent or 2.4 million people), followed by adults aged 26 or older (2.1 percent or 4.7 million people), then by adolescents aged 12 to 17 (1.3 percent or 347,000 people.”); NAT’L INST. OF HEALTH, NEWS RELEASE (Aug. 22, 2022), <https://www.nih.gov/news-events/news-releases/marijuana-hallucinogen-use-among-young-adults-reached-all-time-high-2021> (“Past-year hallucinogen use had been relatively stable over the past few decades until 2020, when reports of use started to increase dramatically. In 2021, 8% of young adults reported past-year hallucinogen use, representing an all-time high since the category was first surveyed in 1988. By comparison, in 2016, 5% of young adults reported past-year hallucinogen use, and in 2011, only 3% reported use.”).
 71. See David Nutt & Robin Carhart-Harris, *The Current Status of Psychedelics in Psychiatry*, 78 JAMA PSYCHIATRY 121, 122 (2021) (“Why might psychedelics work in such a wide range of disorders? We suggest this may be because these conditions are all internalizing disorders. In depression, patients continually ruminate about their failings, reiterate thoughts of guilt, and engage in self-critical inner narratives. In addition, drug craving drives behavior that is specific, narrow, and rigid; individuals with addiction ruminate on the drug, including where to get it, how to pay for it, etc. In obsessive-compulsive disorder and anorexia, there is excessive rumination about threats to the person, from contamination or the effects of eating or overeating, respectively. Neuroimaging studies reveal that psychedelics probably work by disrupting brain systems and circuits that encode these repetitive thoughts and behaviors. The psychedelic experience opens a therapeutic window that disrupts entrenched thinking and allows insight, which with psychotherapeutic support can lead to a recalibration of one’s spectrum of associations.”) (endnote omitted).
 72. See, e.g., GRINSPOON & BAKALAR, *supra* note 1; STANISLAV GROF, REALMS OF THE HUMAN UNCONSCIOUS: OBSERVATIONS FROM LSD RESEARCH (2019); STANISLAV GROF, LSD PSYCHOTHERAPY: THE HEALING POTENTIAL OF PSYCHEDELIC MEDICINE (2008); OLIVER RUMIE HOVMAND, MEDICAL PSYCHEDELICS: THE EVIDENCE-BASED TEXTBOOK (2008); RICHARD LOUIS MILLER, PSYCHEDELIC MEDICINE: THE HEALING POWERS OF LSD, MDMA, PSILOCYBIN, AND AYAHUASCA (2017); MOGHADDAM, *supra* note 33; PASSIE, *supra* note 44; MICHAEL POLLAN, HOW TO CHANGE YOUR MIND: WHAT THE NEW SCIENCE OF PSYCHEDELICS TEACHES US ABOUT CONSCIOUSNESS, DYING, ADDICTION, DEPRESSION, AND TRANSCENDENCE (2019); PSYCHEDELICS AND PSYCHOTHERAPY: THE HEALING POTENTIAL OF EXPANDED STATES (Tim Read et al. eds., 2021); BEN SESSA, THE PSYCHEDELIC RENAISSANCE: REASSESSING THE ROLE OF PSYCHEDELIC DRUGS IN 21ST CENTURY PSYCHIATRY AND SOCIETY (2018); RICK STRASSMAN, THE PSYCHEDELIC HANDBOOK: A PRACTICAL GUIDE TO PSILOCYBIN, LSD, KETAMINE, MDMA, AND AYAHUASCA (2022); Peter S. Hendricks et al., *Psilocybin, Psychological Distress, and Suicidality*, 29 J. PSYCHOPHARMACOLOGY 1041 (2015); Peter S. Hendricks et al., *Classic Psychedelic Use Is Associated with Reduced Psychological Distress and Suicidality in the United States Adult Population*, 29 J. PSYCHOPHARMACOLOGY 280 (2015); Andrew Jacobs, *The Psychedelic Revolution Is Coming. Psychiatry May Never Be the Same*, N.Y. TIMES, May 9, 2021, <https://www.nytimes.com/2021/05/09/health/psychedelics-mdma-psylocybin-molly-mental-health.html?smid=nytcore-ios-share&referringSource=articleShare>.
 73. Andrea Cipriani et al., *Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults with Major Depressive Disorder: A Systematic Review and Network Meta-Analysis*, 391 LANCET 1357, 1358 (2018); Guy Goodwin et al., *Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression*, 387 NEW ENG. J. MED. 1637, 1638 (2022) (“Treatment-resistant depression is a challenging disorder to treat, as shown in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Incidences of remission became progressively lower from the first course of antidepressant treatment (36.8%) to the second course (30.6%), third course (13.7%), and fourth course (13.0%). Failure of two courses of treatment has generally been considered to define a group of patients who have treatment-resistant depression. Patients with treatment-resistant depression have greater severity and duration of illness, disability, physical illness, incidences of hospitalization, risk of suicide, and economic costs than patients with treatment-responsive depression.”) (endnotes omitted); Bertha K. Madras, *Psilocybin in Treatment-Resistant Depression*, 387 New

- ENG. J. MED. 1708, 1708 (2022) (“Depression ranks first among psychiatric disorders that dominate the global burden of disease, posing a substantial personal strain and economic drain on nations.”).
74. Emil F. Coccaro, *New Hope for Patients with Major Depressive Disorder?*, 381 NEW ENG. J. MED. 980, 980 (2019) (“Major depressive disorder is a serious mental health condition that affects up to 16% of people in the United States during their lifetimes and about 7% of the U.S. population in a given year. In addition, patients with major depressive disorder have an outsized risk of suicidal behavior.”) (endnote omitted).
 75. *Investors Hope Psychedelics Are the New Cannabis. Are They High?*, ECONOMIST, Oct. 19, 2019, <https://www.economist.com/business/2019/10/19/investors-hope-psychedelics-are-the-new-cannabis-are-they-high> [hereafter *Investors*].
 76. MOGHADDAM, *supra* note 33, at 68, 152; *Investors*, *supra* note 75.
 77. MOGHADDAM, *supra* note 33, at 152; see Ying Jiang et al., *The Correlation of Esketamine with Specific Adverse Events: A Deep Dive into the FAERS Database*, EUROPEAN ARCHIVES PSYCHIATRY & CLINICAL NEUROSCIENCE 10.1007/s00406-023-01732-5, at 1 (2023) (“Depressive disorder is a prevalent mental illness, with over 300 million sufferers worldwide. In China, the lifetime prevalence rate for depressive disorders stands at 6.8%. Even more concerning, 15% of patients with severe depression exhibit suicidal behaviors, and 3.4% eventually succumb to suicide, leading to a significant socio-familial burden....”) (endnotes omitted).
 78. Robin L. Carhart-Harris, *Psilocybin with Psychological Support for Treatment-Resistant Depression: An Open-Label Feasibility Study*, 3 LANCET PSYCHIATRY 619, 620 (2016); *Investors*, *supra* note 75 (noting an estimate that “mental-health disorders could cost the global economy \$16trn by 2030”).
 79. U.S. FOOD & DRUG ADMIN., DEPRESSION MEDICINES (2019), <https://www.fda.gov/consumers/womens-health-topics/depression-medicines>.
 80. MOGHADDAM, *supra* note 33, at 68; Madras, *supra* note 73, at 1708. The medications first used to treat depression—monoamine oxidase (MAO) inhibitors and tricyclic antidepressants—were serendipitously discovered in the 1950s but are no longer used to treat depression because of their potential adverse side effects. Lieberman, *supra* note 62, at 1460; see also Nutt et al., *supra* note 52, at 24. Newer treatments—selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine uptake inhibitors (SNRIs) have replaced MAO inhibitors and tricyclics because they have fewer potentially serious side effects. MOGHADDAM, *supra* note 33, at 81–83; Nutt et al., *supra* note 52, at 24. Still, we do not know exactly how SSRIs and SNRIs operate at a molecular level. Grob & Grigsby, *supra* note 1, at xi; MOGHADDAM, *supra* note 33, at 84–87; Catherine J. Harmer et al., *How do Antidepressants Work? New Perspectives for Refining Future Treatment Approaches*, 4 LANCET PSYCHIATRY 409 (2017) (discussing theories).
 81. Nutt et al., *supra* note 52, at 24. A quasi-exception exists for ketamine, a dissociative drug (and technically not a psychedelic) that the U.S. Food and Drug Administration (FDA) approved in 1970 for use as a battlefield anaesthetic and approved in 2019 as a treatment of MDD. MOGHADDAM, *supra* note 33, at 17–18, 84–87. (The FDA must preapprove the distribution of new drugs in interstate commerce. See Paul J. Larkin, *Twenty-First Century Illicit Drugs and Their Discontents: Why the FDA Could Not Approve Raw Cannabis as a “Safe,” “Effective,” and “Uniform” Drug*, HERITAGE FOUND., Special Report No. 275 (2023).) Major news outlets touted the FDA’s approval as “the biggest advance for depression in years.” MOGHADDAM, *supra* note 33, at xi (punctuation omitted). Ketamine was not a new drug, however; it was an approved drug that received a different approval for a new use and has become an accepted MDD treatment. More than 100 American and European clinics administer it. Loder, *supra* note 44.
 82. PTSD is a similar affliction. SSRIs are the “first line” PTSD medications, but “an estimated 40–60% of patients do not respond to these compounds.” *Id.* (footnote omitted). Approximately 5 percent of the American population is afflicted with PTSD, such as military personnel, veterans, first responders, and certain minority groups. Jennifer M. Mitchell et al., *MDMA-Assisted Therapy for Moderate to Severe PTSD: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study*, 29 NATURE MEDICINE 2473, 2473, 2474 (2023) [hereafter Mitchell et al., *MDMA and Moderate-to-Severe PTSD*].
 83. “Hallucinogen” is the term used in medical parlance in the 1950s, but “psychedelic” is the popular term nowadays. Grob & Grigsby, *supra* note 1, at ix–x. Psilocybin, mescaline, lysergic acid diethylamide (LSD), and dimethyltryptamine (DMT) are the “classic” or “serotonergic” psychedelics. *Id.* at x.
 84. See Nutt & Carhart-Harris, *supra* note 71, at 121 (“The past decade has seen a resurrection in human psychedelic drug research, especially involving psilocybin. There were 2 drivers to this. The first was the discovery by Griffiths et al that a single high dose (25 mg) of psilocybin, given in a psychotherapeutic setting, produced enduring positive changes in mood and well-being in people who do not have depression. The second was our series of neuroimaging studies in healthy volunteers, which revealed that psilocybin produced profound and meaningful alterations in brain function, especially of the default mode network, consistent with an antidepressant effect. These findings suggested the possible utility of psilocybin for treating depression and initiated the launch of studies in the UK and US that further supported an antidepressant outcome from a single, 25-mg psilocybin dose in people with resistant depression and those with anxiety and depression symptoms provoked by life-threatening cancer diagnoses. There have also been open studies showing efficacy in both alcohol and tobacco dependence.”) (endnotes omitted).
 85. Grob & Grigsby, *supra* note 1, at xi; see also, e.g., Hamer, *supra* note 15; Marks & Cohen, *supra* note 15, at 1670. Psychedelics are still used for that purpose in some religions. See *supra* note 15.
 86. Ethan Nadelmann, *Preface* (1997 Edition), in GRINSPOON & BAKALAR, *supra* note 1.
 87. Psilocybin (or 4-phosphoryloxy-N,N-dimethyltryptamine) is the ingredient found in certain mushrooms. The body metabolizes it into psilocin, which attaches to serotonin receptors and triggers hallucinogenic activity. Grob et al., *supra* note 52, at 71; see Giovanni Martinotti et al., *Hallucinogen Persisting Perception Disorder: Etiology, Clinical Features, and Therapeutic Perspectives*, 8 BRAIN SCI. 47, 47 (2018) (“The hallucinogenic properties of many natural products were known for thousands of years: popular healers, ‘brujos’, and shamans used these substances in ancient times for medical, religious, spiritual, ritual, divination, and magical purposes.”).
 88. ALBERT HOFFMAN, *LSD: MY PROBLEM CHILD* (4th ed. 2017).

89. See PASSIE, *supra* note 44, at 2.
90. In addition to the articles cited elsewhere in this *Special Report*, see, for example, Florence Butlen-Ducuing et al., *The Therapeutic Potential of Psychedelics—The European Regulatory Perspective*, 401 LANCET 714 (2023); Robin Carhart-Harris et al., *Trial of Psilocybin Versus Escitalopram for Depression*, 384 NEW ENG. J. MED. 1402 (2021); Robin L. Carhart-Harris et al., *LSD Enhances Suggestibility in Healthy Volunteers*, 232 PSYCHOPHARMACOLOGY 785 (2015); Alan K. Davis et al., *Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder A Randomized Clinical Trial*, 78 JAMA PSYCHIATRY 481 (2021); Gregor Hasler, Correspondence, *Psychotherapy and Psychedelic Drugs*, 10 LANCET PSYCHIATRY 167 (2023); David J. Heal et al., *Psychedelics: Threshold of a Therapeutic Revolution*, 236 NEUROPHARMACOLOGY 109610 (2023); Kelly Morris, *Research on Psychedelics Moves into the Mainstream*, 371 LANCET 1491 (2008); Torsten Passie et al., *The Pharmacology of Psilocybin*, 7 ADDICTION BIOLOGY 357 (2002); Stephen Ross et al., *Rapid and Sustained Symptom Reduction Following Psilocybin Treatment for Anxiety and Depression in Patients with Life-Threatening Cancer: A Randomized Controlled Trial*, 30 J. PSYCHOPHARMACOLOGY 1165 (2016); James J. Rucker et al., *The Effects of Psilocybin on Cognitive and Emotional Functions in Healthy Participants*, 36 J. PSYCHOPHARMACOLOGY 114 (2022); Ben Sessa, *Shaping the Renaissance of Psychedelic Research*, 380 LANCET 200 (2012); Otto Simonsson et al., *Associations Between Lifetime Classic Psychedelic Use and Markers of Physical Health*, 35 J. PSYCHOPHARMACOLOGY 447 (2021); William R. Smith & Paul S. Applebaum, *Novel Ethical and Policy Issues in Psychiatric Uses of Psychedelic Substances*, 216 NEUROPHARMACOLOGY 109165 (2022); Solomon H. Snyder, *Seeking God in the Brain—Efforts to Localize Higher Brain Functions*, 358 NEW ENG. J. MED. 6 (2008); Dan Xi et al., *National Institutes of Health Psilocybin Research Speaker Series: State of the Science, Regulatory and Policy Landscape, Research Gaps, and Opportunities*, 230 NEUROPHARMACOLOGY 109467 (2023); cf. Jonathan Perry, *Mending Invisible Wounds: The Efficacy and Legality of MDMA-Assisted Psychotherapy in United States' Veterans Suffering with Post-Traumatic Stress Disorder*, 29 J.L. & HEALTH 272 (2016).
91. *Psychedelic-Assisted Psychotherapy: Hope and Dilemma*, 32 LANCET REGIONAL HEALTH—EUROPE, Sept. 23, 2023, [https://www.thelancet.com/journals/lanep/article/PIIS2666-7762\(23\)00146-1/fulltext](https://www.thelancet.com/journals/lanep/article/PIIS2666-7762(23)00146-1/fulltext) [hereafter *Psychedelic Hope and Dilemma*] (“[C]urrently 127 clinical trials for psilocybin and 88 for MDMA [3,4-methylenedioxymethamphetamine] are listed on ClinicalTrials.gov, not only for PTSD and Depression, but also for various other conditions, including alcohol use disorders, addiction, social anxiety, and enhancement of spirituality.”); see, e.g., Madras, *supra* note 73, at 1709 (“[M]ore than 180 clinical trials of psilocybin, MDMA . . . or LSD to treat depression, other neuropsychiatric disorders, substance use disorders, demoralization (hopelessness, inability to cope, and allied feelings of inadequacy), and enhancement of spirituality are currently listed on ClinicalTrials.gov.”) (footnote omitted); *Investors, supra* note 75 (“In October last year America’s Food and Drug Administration granted Compass Pathways ‘breakthrough therapy’ designation, which fast-tracks the approval process. The company is using the \$38m it has raised to run the largest clinical study of psilocybin ever. Ekaterina Malievskaia, its co-founder, hopes that the therapy could go on sale within five years ‘if everything works out’, including the science. Patients would receive carefully controlled doses in one-off, therapist-run sessions. These may last all day and cost \$1,000 a pop. Field Trip Ventures, a Canadian startup, plans to open speciality clinics where they could be administered (and clinical trials conducted).”).
92. Such as the Multidisciplinary Association for Psychedelic Studies (MAPS), <https://maps.org>, an organization created in 1986 in the wake of the prohibition of MDMA for the purpose of investigating that drug’s use in psychedelic therapy. Sessa, *supra* note 72, at 16. MAPS recently submitted MDMA to the FDA for approval as an adjunct to psychotherapy for PTSD. See *infra* note 104.
93. See, e.g., IMPERIAL COLLEGE LONDON, CENTRE FOR PSYCHEDELIC RSCH. (undated), <https://www.imperial.ac.uk/psychedelic-research-centre/> (last visited Dec. 5, 2023); QUEENS UNIV., HEALTH SCIENCES (2023), <https://healthsci.queensu.ca/research/psychedelics>.
94. See, e.g., JOHNS HOPKINS CNTR. FOR PSYCHEDELIC & CONSCIOUSNESS RSCH. (undated), <https://hopkinspsychedelic.org> (last visited Dec. 5, 2023); UNIV. OF MICHIGAN MEDICAL SCHOOL PSYCHEDELIC CNTR. (M-PSYC) (undated), <https://michiganpsychedelic.med.umich.edu>; Mt. SINAI ICAHN SCHOOL OF MEDICINE CNTR. FOR PSYCHEDELIC PSYCHOTHERAPY AND TRAUMA RSCH. (undated), <https://icahn.mssm.edu/research/center-psychedelic-psychotherapy-trauma-research>; NYU LANGONE CENTER FOR PSYCHEDELIC MEDICINE STANFORD UNIV. PSYCHEDELIC STUDY GROUP (2023), <https://med.stanford.edu/spsg.html>; UNIV. OF TEXAS AT AUSTIN DELL MEDICAL SCHOOL CNTR. FOR PSYCHEDELIC RSCH. & THERAPY (2023), <https://dellmed.utexas.edu/units/center-for-psychedelic-research-and-therapy>; UNIV. OF CALIFORNIA, BERKELEY, CNTR. FOR THE SCIENCE OF PSYCHEDELICS (2023), <https://psychedelics.berkeley.edu/>; UNIV. OF CALIFORNIA DAVIS INST. FOR PSYCHEDELICS AND NEUROTHERAPEUTICS (2023), <https://neurotherapeutics.ucdavis.edu>; UNIV. OF WISCONSIN—MADISON TRANSDISCIPLINARY CNTR. FOR RSCH. IN PSYCHEDELIC SUBSTANCES (undated), <https://research.pharmacy.wisc.edu/tcrps/>; YALE SCHOOL OF MEDICINE, PSYCHIATRY, PROGRAM FOR PSYCHEDELIC STUDIES (2023), https://medicine.yale.edu/psychiatry/research/programs/clinical_people/psychedelic/; *Investors, supra* note 75.
95. FOOD & DRUG ADMIN., CNTR. FOR DRUG EVALUATION & RESEARCH, PSYCHEDELIC DRUGS: CONSIDERATIONS FOR CLINICAL INVESTIGATIONS, GUIDANCE FOR INDUSTRY, DRAFT GUIDANCE (June 2023) [hereafter FDA PSYCHEDELIC GUIDANCE]. Some of the guidance is standard for any drug trial. For instance, “[s]ponsors must provide sufficient chemistry, manufacturing, and controls information to ensure proper identification, quality, purity, and strength of the investigational drug substance and drug product. This is true for all phases of clinical trials.” *Id.* at 2 (footnote omitted). Sponsors must comply with all Drug Enforcement Administration regulations governing the importation, manufacturing, and storage of Schedule I drugs. *Id.* at 6. Insofar as plant material is used in creating a psychedelic—as occurs in the case of psilocybin, mescaline, or ayahuasca—drug sponsors should consider the FDA’s guidance document for botanical drug development. *Id.* at 3 (citing FOOD & DRUG ADMIN., CNTR. FOR DRUG EVALUATION & RSCH., FOOD & DRUG ADM’N, BOTANICAL DRUG DEVELOPMENT: GUIDANCE FOR INDUSTRY (Dec. 2016)).
96. Some researchers have offered quite extravagant testimonials on behalf of psychedelics. See Nutt, *supra* note 21, at 85 (quoting Dr. Stanislav Grof: “Psychedelics, used responsibly and with caution, would be for psychiatry what the microscope is for biology and medicine, or the telescope for astronomy.”).
97. U.S. FOOD & DRUG ADMIN., Press Announcement, *FDA Approves New Nasal Spray Medication for Treatment-Resistant Depression; Available Only at a Certified Doctor’s Office or Clinic*, Mar. 5, 2019 [hereafter FDA Ketamine Approval], <https://www.fda.gov/news-events/press-announcements/fda>

- approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified (“The U.S. Food and Drug Administration today approved Spravato (esketamine) nasal spray, in conjunction with an oral antidepressant, for the treatment of depression in adults who have tried other antidepressant medicines but have not benefited from them (treatment-resistant depression). Because of the risk of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration, and the potential for abuse and misuse of the drug, it is only available through a restricted distribution system, under a Risk Evaluation and Mitigation Strategy (REMS).”); see also U.S. DRUG ENFORCEMENT ADMIN., DRUG FACT SHEET: KETAMINE (Apr. 2020), <https://www.dea.gov/sites/default/files/2020-06/Ketamine-2020.pdf> (“Ketamine is a dissociative anesthetic that has some hallucinogenic effects. It distorts perceptions of sight and sound and makes the user feel disconnected and not in control. It is an injectable, short-acting anesthetic for use in humans and animals. It is referred to as a ‘dissociative anesthetic’ because it makes patients feel detached from their pain and environment. Ketamine can induce a state of sedation (feeling calm and relaxed), immobility, relief from pain, and amnesia (no memory of events while under the influence of the drug). [¶] It is abused for its ability to produce dissociative sensations and hallucinations. [¶] Ketamine has also been used to facilitate sexual assault.”); Bravo, *supra*, in Grob & Grigsby, *supra* note 1, at 330; Jiang et al., *supra* note 77, at 1 (“Since the discovery of rapid antidepressant effects in 2000, ketamine, R-ketamine, and Esketamine [the last two are enantiomers, or mirror images, of each other] have emerged as breakthrough directions in depression research. Ketamine and its enantiomer—especially Esketamine—have displayed groundbreaking potential in treating depression.... Particularly when administered intravenously, Esketamine demonstrates fast and prominent antidepressant results, with efficacy rates of 50.0%, 48.2%, and 43.7% at 24 h, 72 h, and 7 days, respectively.... However, IV administration necessitates specific medical environments, potentially hindering patient compliance. Addressing this concern, the U.S. Food and Drug Administration (FDA) approved the Esketamine nasal spray Spravato in March 2019. Designed for use alongside oral antidepressants, this nasal spray is intended for adults struggling with treatment-resistant depression.... By August 2020, this medication also garnered a new indication for treating adults with depression accompanied by suicidal ideation or behavior....”) (endnotes omitted); *id.* at 4 (“Clinical trials have shown that, whether through intravenous injection or nasal administration, Esketamine can rapidly produce antidepressant effects. As an adjunct therapy, nasal administration twice a week can produce effects similar to intravenous injection....”) (endnotes omitted).
98. Like ketamine, psilocybin takes effect quickly, but unlike ketamine, psilocybin has the potential for a longer-lasting effect: several months versus one–two weeks. Ross et al., *supra* note 29, at 186; see also *Psychedelic Medicines*, *supra* note 10 (“The coming year will see a number of milestones in the emerging era of psychedelic medicines. The recreational drug MDMA will complete a second phase-3 trial for the treatment of post-traumatic stress disorder (PTSD). If this trial confirms the findings of the first, from 2021, then in 2023 MDMA will be considered by America’s Food and Drug Administration for approval. MAPS, a public-benefit corporation, has so far shown that three doses of MDMA, along with a course of therapy over 18 weeks, can deliver a significant reduction in the symptoms of PTSD.... MDMA, ketamine and conventional psychedelic drugs, such as psilocybin and LSD, all have one thing in common: they cause rapidly acting changes in brain function. They trigger receptors such as those for serotonin, and thereafter a cascade of signals important for the growth of neurons. It is probably not necessary to cause hallucinations to create the sort of neuronal plasticity that is increasingly thought to be important in the treatment of brain disorders. One theory is that many psychiatric and neurodegenerative conditions are a result of ‘cortical atrophy’, the loss of connectivity between the connections of neurons in the pre-frontal cortex. Psychedelics seem to allow these connections to be strengthened and reconnected.”).
99. As NIDA Director Volkow has explained: “Challenges notwithstanding, the promise of psychedelics research goes beyond the promise of new pharmacotherapies. Declining life expectancy among US residents in recent years has been tied to despair—overdoses, suicides, and diseases attributable to alcohol misuse all reflect large swaths of society feeling increased pain and loss of connection. We know a great deal about what goes awry in the brains of people with mental illnesses including substance use disorders, but we know less about what goes right in the brains of people whose lives are full of meaning and connection and who may be more resilient to the development of psychiatric conditions. Better understanding of the mechanisms by which psychedelics may increase resilience could be highly valuable. Besides telling us about the neurobiology of resilience, such research might facilitate development of alternative treatment modalities ([e.g.,] neuromodulation) that could produce similar benefits for patients.” Volkow, *supra* note 62, at 980.
100. Madras, *supra* note 73, at 1708.
101. Lieberman, *supra* note 62.
102. That designation expedites the review process for important drugs materially better at treating a serious condition than existing therapies. “Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). [¶] To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy.” U.S. FOOD & DRUG ADMIN., BREAKTHROUGH THERAPY (2018); see Heal et al., *supra* note 90, at 1.
103. Heal et al., *supra* note 90, at 1.
104. MAPS Public Benefit Corp., *MAPS PBC Announces Submission of New Drug Application to the FDA for MDMA-Assisted Therapy for PTSD*, Dec. 12, 2023, <https://mapsbcorp.com/news/mdma-for-ptsd-fda-submission/>. According to psychiatrist David Nutt, different brain regions encode the factual and emotional components of a traumatic experience. MDMA dampens the emotional region so that a person can recall what happened without the fear or trauma emotionally overwhelming someone. Nutt, *supra* note 21, at 176–77. The sponsor relied in part on two studies that found a beneficial effect from MDMA treatment. See Mitchell et al., *MDMA and Severe PTSD*, *supra* note 23, at 1031 (“Here, we demonstrate that three doses of MDMA given in conjunction with manualized therapy over the course of 18 weeks results in a significant and robust attenuation of PTSD symptoms and functional

impairment as assessed using the CAPS-5 [Clinician-Administered PTSD Scale, AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL (5th ed. 2013)] and SDS [Sheehan Disability Scale], respectively. MDMA also significantly mitigated depressive symptoms as assessed using the BDI-II. Of note, MDMA did not increase the occurrence of suicidality during the study.”), 1032 (“MDMA-assisted therapy induces rapid onset of treatment efficacy, even in those with severe PTSD, and in those with associated comorbidities including dissociative PTSD, depression, history of alcohol and substance use disorders, and childhood trauma. Not only is MDMA-assisted therapy efficacious in individuals with severe PTSD, but it may also provide improved patient safety. Compared with first-line pharmacological and behavioral therapies, MDMA-assisted therapy has the potential to dramatically transform treatment for PTSD and should be expeditiously evaluated for clinical use.”); Mitchell et al., *MDMA and Moderate-to-Severe PTSD*, *supra* note 82, at 2477 (“This confirmatory phase 3 trial showed consistent benefits of MDMA-AT in an ethnically diverse group of individuals with longstanding moderate to severe PTSD and numerous comorbidities. The dropout rate was low, and treatment was generally well tolerated. These findings represent the culmination of over two decades of research, and, together with MAPP1, indicate that further consideration of this treatment in individuals with moderate to severe PTSD is warranted.”) (footnote omitted); see also, e.g., Tracie White, *Falling for Psychedelics*, *STANFORD* 52 (Mar. 2023) (“What we observed with [X’s] scans were too many connections in an area of the brain called the default mode network,” [Leanne Williams, professor of psychiatry and behavioral science, Stanford Center for Cognitive and Neurobiological Imaging] says, referring to a part of the brain in which increased connectivity can result in brooding and in negative self-thoughts. ‘I think in terms of the analogy of when you are in your car, in neutral and just idling,’ Williams says. ‘You are trying to go somewhere, but the car is just stuck.’ In [X’s] post-dosing [brain] scans, the default mode network is less connected—in other words, unstuck. ‘It’s visible, the change.’ [¶] There are other ways of reducing that hyperconnectivity of brain regions over time, including mindfulness meditation, exercise, and antidepressants. But what’s unique to psychedelics is how rapidly such a dramatic change can happen. [¶] While psilocybin can affect the default mode network, MDMA (the drug associated with prosocial feelings of friendliness and empathy) appears to work in multiple areas of the brain, including the amygdala, part of the limbic system that encompasses some of the oldest regions of the brain, Williams says. The amygdala is known to elicit fear in the face of potential threats, activating the fight or flight reaction. If it stays switched on, it can result in some forms of persistent depression or PTSD. ‘With MDMA we see a striking reduction in that region,’ Williams says. ‘People say they feel a deeper understanding, gratitude, a connecting with the planet. I think of psilocybin as dissolving that hyperfocus on internal thoughts and MDMA as dissolving these defenses.’”).

105. MDMA is currently in CSA Schedule I, so it would need to be rescheduled before it could be prescribed. The CSA defines the factors that the Attorney General, and now his designee, the Administrator of Drug Enforcement, must consider when deciding whether and where a drug should be scheduled or rescheduled. See 21 U.S.C. § 811(c) (2018) (“In making any finding under subsection (a) of this section or under subsection (b) of section 812 of this title, the Attorney General shall consider the following factors with respect to each drug or other substance proposed to be controlled or removed from the schedules: [¶] (1) Its actual or relative potential for abuse. [¶] (2) Scientific evidence of its pharmacological effect, if known. [¶] (3) The state of current scientific knowledge regarding the drug or other substance. [¶] (4) Its history and current pattern of abuse. [¶] (5) The scope, duration, and significance of abuse. [¶] (6) What, if any, risk there is to the public health. [¶] (7) Its psychic or physiological dependence liability. [¶] (8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.”). The FDA considers those factors when making scheduling (or rescheduling) recommendations for the Attorney General. See Silvia N. Calderon et al., *Considerations in Assessing the Abuse Potential of Psychedelics During Drug Development*, 224 *NEUROPHARMACOLOGY* 109352, at 3 (2023). For a discussion of the FDA review process, who is involved in it, and the FDA’s interpretation of the terms “potential for abuse,” “addiction-forming or addiction-sustaining liability,” and “dependence,” which are used in but are undefined by the CSA, see, for example, U.S. FOOD & DRUG ADMIN., CNTR. FOR DRUG EVALUATION & RESEARCH RSCH. (CDER), *ASSESSMENT OF ABUSE POTENTIAL OF DRUGS: GUIDANCE FOR INDUSTRY* (2020); Calderon et al., *supra*, at 2–3; Jack E. Henningfield et al., *Psychedelic Drug Abuse Potential Assessment Research for New Drug Applications and Controlled Substances Act Scheduling*, 218 *NEUROPHARMACOLOGY* 109220 (2022); Johnson et al., *supra* note 48.
106. In 2020 and 2022, respectively, Oregon and Colorado voters passed two relevant drug decriminalization initiatives. Oregon Measures 109 and 110, respectively, permitted psilocybin to be used for medical treatment purposes and decriminalized possession of small amounts of all drugs, including “hard” drugs, such as illicit fentanyl and methamphetamine, in favor of fines with a maximum of \$100 or a health assessment. See OR. REV. STAT. ch. 475A, §§ 475a.590–475a.722 (West 2023); Donald Morrison, *Oregon Votes to Decriminalize All Drugs, Allow Psilocybin for Mental-Health Treatment*, *WALL ST. J.*, Nov. 4, 2020, <https://www.wsj.com/articles/oregon-votes-to-decriminalize-all-drugs-allow-psilocybin-for-mental-health-treatment-11604477494>; *Sensible Policy on Psychedelic Drugs Is Growing More Common*, *ECONOMIST*, Jan. 29, 2022, <https://www.economist.com/united-states/2022/01/29/sensible-policy-on-psychedelic-drugs-is-growing-more-common> [hereafter *Psychedelic Policy*]. (Early in March 2024, the Oregon legislature revisited drug policy generally, passing legislation making criminal once again the possession of drugs such as fentanyl and cocaine. The governor signaled that she would sign the bill. Kevin Sabet, *Oregon Makes a U-Turn on Drug Decriminalization*, *WALL ST. J.*, Mar. 6, 2024, <https://www.wsj.com/articles/oregon-makes-a-u-turn-on-drug-decriminalization-cede4a40>; Conrad Wilson, *Oregon Governor Will Sign Bill to Recriminalize Drugs, Expand Treatment*, *OR. PUB. BROADCASTING*, Mar. 8, 2024, <https://www.opb.org/article/2024/03/08/oregon-governor-tina-kotek-bill-ending-drug-decriminalization-expand-treatment/>.) Colorado voters passed a similar law in 2022. Natural Medicine Health Act of 2022 (codified at COLO. REV. STAT. ANN. Art. 170, §§ 12-170-102 to 12-170-117 (West 2023)); see Mason Marks, *State-Regulated Psychedelics on a Collision Course with FDA*, *JAMA ONLINE E1* (2023) (“In addition to psilocybin, Colorado’s program may offer other psychedelics such as mescaline, ibogaine, and dimethyltryptamine. [¶] Other states, including New York, Massachusetts, Vermont, Illinois, and California, will consider similar legislation in 2024.”); *infra* note 209.

The Oregon and Colorado laws cannot exempt the distribution of psychedelics from federal law. See *Gonzalez v. Raich*, 545 U.S. 1 (2005); *United States v. Oakland Cannabis Buyers’ Cooperative*, 532 U.S. 483 (2001). Because the Oregon law went into effect in the summer of 2023, the federal-state “train wreck” that our nation’s cannabis laws have become, see Stuart Taylor, Jr., *Marijuana Policy and Presidential Leadership: How to Avoid a Federal-State Train Wreck*, *GOVERNANCE STUDIES AT BROOKINGS INST.* 3 (Apr. 2013) (*Spoiler Alert: We didn’t.*), now has a counterpart in psychedelics, Marks, *supra*, at E1 (“[S]tate lawmakers often overlook the shortcomings of this approach. In addition to being expensive, redundant, and potentially

misleading, many state-regulated psychedelic programs are on a collision course with FDA law.”). Despite the willful blindness that the federal government has manifested regarding the states’ blatant, widespread violation of the federal cannabis laws, see Paul J. Larkin, Jr., *Reflexive Federalism*, 44 HARV. J.L. & PUB. POL’Y 523, 530–42 (2021), the FDA and Drug Enforcement Administration might prove unwilling to allow parties to flout federal law on psychedelics regardless of what state law provides, see Marks, *supra*, at E1 (“Congress, courts, and federal agencies consider psychedelics Schedule I controlled substances with no currently accepted medical use and a high potential for abuse. Outside narrow exceptions for research, the production, possession, and sale of psychedelics are federal felonies. Consequently, state-licensed psychedelic businesses violate federal law when producing or dispensing psilocybin... [S]ome businesses ignore these [state-law] restrictions [such as a ban on advertising of psilocybin as a medical treatment] and advertise their services as treatments for depression or addiction. In addition to violating Oregon law, this practice conflicts with federal laws such as the Federal Food, Drug, and Cosmetic Act, which governs the FDA. As a public health agency that protects consumers against health misinformation, the FDA may be obliged to intervene.”) (footnotes omitted). Some cities, such as Denver, Detroit, the District of Columbia, Oakland, and Santa Cruz, have passed measures legalizing use of psilocybin for treatment or directing the locals to ignore those laws. *Id.*; Ernesto Londono, *Minneapolis Mayor Loosens Enforcement of Psychedelics*, N.Y. TIMES, July 21, 2023, <https://www.nytimes.com/2023/07/21/us/minneapolis-mayor-psychedelics.html?searchResultPosition=2> (“Mayor Jacob Frey of Minneapolis issued an executive order on Friday instructing the city’s police officers to, in essence, look the other way when it comes to the purchase and use of certain illegal psychedelic drugs.”); *Psychedelic Policy*, *supra* note 106 (“At least ten cities have made psychedelics a low priority for law enforcement.”). As far as federal law is concerned, municipalities are merely corporations created by the states. See *Monell v. New York City Dep’t of Soc. Servs.*, 436 U.S. 658, 664, 673 n.30, 686–89 (1978). The upshot is that, unless a state grants its cities permission to opt out of state laws, municipalities cannot nullify a parent state’s law. Also, no municipality can “flip off” federal law regardless of what a state law might authorize. Local ordinances, much like “sanctuary city” designations, are just “virtue signaling” exercises.

107. See Larkin, *supra* note 106, at 530–32, 536–42.
108. Perhaps in 2024. See Loder, *supra* note 44; Dana G. Smith, *What Does Good Psychedelic Therapy Look Like?*, N.Y. TIMES, June 5, 2023, <https://www.nytimes.com/2023/06/03/well/mind/psychedelic-therapy.html?searchResultPosition=1> (“[T]he Food and Drug Administration is expected to approve it and MDMA, or Ecstasy, to treat depression and post-traumatic stress disorder by 2024.”) [hereafter Smith, *Good Psychedelic Therapy*].
109. Consider this summary of the two teams: “The discourse surrounding the application of psychedelic-assisted psychotherapy for clinical use has created a dilemma and sparked debate among mental health professionals, researchers, and patrons of psychedelics, effectively dividing them into two factions: those who endorse this innovative treatment and those who are sceptical. Both sides are supported by equally valid arguments. On one hand, proponents emphasize the long-lasting positive effect of the treatment and meaningful progress after just one treatment. On the other hand, critics draw attention to the paucity of substantial evidence due to small sample sizes in trials, the absence of clarity regarding ideal candidates for this treatment, and potential for adverse experiences in some patients, leading to exacerbated psychological challenges, commonly referred to as so-called ‘bad trips.’” *Psychedelic Hope and Dilemma*, *supra* note 91; see also, e.g., Madras, *supra* note 73; Pollan, *supra* note 56 (“This is not to say that ‘bad trips’ don’t happen; they do, especially when the drugs are used carelessly. People at risk for schizophrenia sometimes have psychotic breaks on psychedelics, and people surely do stupid things under the influence that can get them killed. But the more extreme claims about LSD—that it scrambled users’ chromosomes or induced them to stare at the sun until blind—were debunked long ago.”).
110. See GRINSPOON & BAKALAR, *supra* note 1, at 234–35 (“Psychedelic drugs are used not as chemotherapy but to attain self-knowledge in a way that both resembles and allegedly intensifies the effects of other insight therapies like psychoanalysis, religious disciplines, and the forms of psychiatry referred to as the human potential movement.”). Consider the following explanation of how the joint therapy works in the case of MDMA: “The basic premise of this treatment approach is that the therapeutic effect is not due simply to the psychical effects of the medicine; rather, it is the result of an interaction among the effects of the medicine, the therapeutic setting, and the mindsets of the participants and the therapists. MDMA produces an experience that appears to temporarily reduce fear, increase the range of positive emotions toward self and others, and increase the interpersonal trust without clouding the sensorium or preventing access to emotions. MDMA may catalyze therapeutic processing by allowing participants to stay emotionally engaged while revisiting traumatic experiences, without being overwhelmed by anxiety or other painful emotions. Frequently, participants are able to experience and express fear, anger, and grief as part of the therapeutic process, with less likelihood of either feeling overwhelmed by these emotions or avoiding them by dissociation or emotional numbing.” Mithoefer & Mithoefer, *in* Grob & Grigsby, *supra* note 1, at 249.
111. See GRINSPOON & BAKALAR, *supra* note 1, at 176 (“The most important fact about chronic or long-term psychedelic drug use is that there is very little of it. In the first place, tolerance develops so fast that it is impossible to derive much effect from LSD, mescaline, or psilocybin used more than twice a week without continually increasing the dose. Nor is there any physical addiction or withdrawal syndrome to provide a compelling reason to keep using these drugs. Whether they can be said to create psychological dependence is hard to decide, because psychological dependence is one of those things that everyone thinks he can recognize and no one knows how to define. Almost any habit that satisfies a need or desire, whether related to drugs or not, can be described as a psychological dependence. Some forms of dependence are trivial, some benign. One common sign of an undesirable psychological dependence (of course, not the only one) is that the person who has the habit wishes he could give it up but feels unable to do so; psychedelic drug users almost never feel that way. Some people are especially susceptible to dependence on drugs because of anxiety, depression, feelings of inadequacy, or certain character disorders, but today they are unlikely to choose psychedelic drugs, which do not provide reliable relief. [¶] At the height of the hippie era a number of people used LSD once or twice a week for years; they could be said to be dependent on it in a sense, and certainly some of them were seriously disturbed. But the dependence was cultural rather than chemical: to take LSD constantly was to make a statement of loyalties and to establish a social role. Now that the supporting community and world view no longer exist, there is rarely anything that can be called dependence on psychedelic drugs, and the reason is simple: a drug that takes people into a different stretch of

unfamiliar mental territory for eight hours every time they use it is not for every day or even every weekend. Drug users soon come to understand that psychedelic trips are not to be embarked on lightly, and they tend to stop using LSD or cut down their consumption greatly after a few years. The kind of steady, reliable euphoria that produces a drug habit is impossible to achieve with psychedelic drugs; to speak of a craving for them would be absurd. So chronic or long-term use does not have the same meaning for LSD that it has for drugs of habit....", 179 ("Psychedelic drug users have also been tested for organic brain damage.... At most, these studies confirm the existence of an eccentric acid head personality; they do not imply mental illness or brain damage."), 227 ("The main danger in psychedelic drug therapy is the same as the danger of any deep-probing psychotherapy: the unconscious material that comes up can be neither accepted nor integrated nor totally repressed, symptoms may become worse, and even psychosis or suicide is possible. But the potential for harm has been exaggerated, for two reasons. First, much irrational fear and hostility is left over from the cultural wars of the sixties. More generally, we tend to misconceive drugs as something utterly different from and almost by definition more dangerous than other ways of changing mental processes; actually, the dangers in work with LSD do not seem obviously greater than in comparable forms of therapy aimed at emotional insight.").

112. See, e.g., *Id.* at 196 ("Psychoanalytic therapy has been recommended to speed up psychoanalysis and psychoanalytically oriented psychotherapy, especially for people with excessively strict super egos and a lack of self-esteem; it has also been used to overcome the resistance of severe chronic neurotics with defenses so rigid that they would be inaccessible to treatment."); Dave King & Jonny Mastell, *The Treatment of Depressive Disorders with Psychedelics*, in Grob & Grigsby, *supra* note 1, at 501–14; Nutt et al., *supra* note 52, at 25–26: "[Psilocybin's] effects on patients suffering from depression were remarkable—e.g., two experiences with psilocybin improved depression scores for weeks, and in some people, years...positioning it as one of the most powerful therapeutics for treatment resistant depression.... [C]urrent medicines suppress symptoms in a similar way that insulin suppresses hyperglycemia in diabetes. Standard antidepressants protect against the stressors that lead to and perpetuate depression, but don't directly access and remedy underlying biopsychosocial causes. In contrast, psychedelic therapy harnesses a therapeutic window opened up by the brain via the effects of the drugs to facilitate insight and emotional release and, with psychotherapeutic support, a subsequent healthy revision of outlook and life-style[.]"; Panik & Presti, *supra*, in Grob & Grigsby, *supra* note 1, at 166 (distinguishing *psychoanalytic therapy*—viz., the use of small doses of LSD (e.g., 25–150 µg) "to loosen psychological defenses and facilitate exploration and processing of emotionally charged material" (known as ego loosening)—from *psychedelic therapy*—viz., the use of larger doses (>200 µg) "with the intention of producing ego dissolution and perhaps a full mystical experience" (known as ego dissolving)); Reynolds, *supra* note 28; Rucker, *supra* note 14; Rachel Yehuda & Amy Lehrner, *Psychedelic Therapy—A New Paradigm of Care for Mental Health*, 330 JAMA 813, 813 (2023) ("When a psychedelic is taken with the proper preparation, intention, facilitation, and therapeutic environment, the patient can use the experience to gain new insights that can catalyze healing and recovery. The psychedelic allows feelings such as self-compassion, forgiveness, understanding, and self-acceptance to surface that can be powerful antidotes to shame, guilt, anger, isolation, disconnection, or other negative emotions that patients find difficult to discuss in therapy and that do not seem to be mitigated by traditional antidepressants. Furthermore, a sense of boundlessness or ego dissolution may be felt as a mystical or spiritual experience, helping people find meaning, perspective, and connection with others and the world. These experiences have been associated with symptom reduction and may represent an important mechanism of action.").
113. See, e.g., Emmanuel A.D. Schindler, *Hallucinogens in a Headache*, in Grob & Grigsby, *supra* note 1, at 515–25 (noting that LSD and psilocybin might prove to be useful treatment at levels below the amount triggering psychedelic effects); White, *supra* note 104.
114. See Nutt, *supra* note 21, at 138–39 (describing how Wilson took the "Belladonna Treatment," which involved complete withdrawal from alcohol and use of a combination of drugs such as scopolamine and hypnotics; quoting Wilson's description of the event: "Suddenly the room lit up with a great white light.... I thought to myself, 'So this is the God of the preachers!' A great peace stole over me.") (footnote omitted).
115. See, e.g., Matthew W. Johnson, *Psychedelics in the Treatment of Addiction*, in Grob & Grigsby, *supra* note 1, at 493 ("[T]he psychedelics may occasion powerfully plastic biological, mental, and behavioral states during or after the period of drug action, in which heightened learning may occur, prompting persistent behavior changes long after the biological effects of the medication have been resolved."); *id.* at 498 ("Whether that pattern of behavior is the self-administration of tobacco, alcohol, cocaine, opioids, or other drugs, or whether it is the cyclical, self-perpetuating thoughts of self-hatred, inevitable failure, or worry that come with mood and anxiety disorders, it may be that psychedelics have the ability to at least temporarily allow one to see outside of those narrow patterns, to recognize the suboptimality of these patterns, and therefore become motivated and learn to adapt to more optimal patterns of living."); Nardou et al., *supra* note 35, at 790 ("During specific periods of brain development, the nervous system exhibits heightened sensitivity to ethologically relevant stimuli, as well as increased malleability for synaptic, circuit and behavioural modifications. These mechanistically constrained windows of time are called critical periods and neuroscientists have long sought methods to reopen them for therapeutic benefit. Recently, we have discovered a novel critical period for social reward learning and shown that the empathogenic psychedelic MDMA is able to reopen this critical period.") (endnote omitted).
116. See, e.g., Passie, *supra* note 44, at 8; Michael P. Bogenschutz et al., *Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients with Alcohol Use Disorder: A Randomized Clinical Trial*, 79 JAMA PSYCHIATRY 953 (2022); Michael P. Bogenschutz & Sarah E. Mennenga, *Classic Psychedelics for Treatment of Alcohol Use Disorder*, in Grob & Grigsby, *supra* note 1, at 482 ("[I]t is possible that psychedelic compounds are providing therapeutic benefit by inducing a temporary state in which the neuroplastic potential of several brain regions is increased. This widespread increase in neuroplastic potential, a nonspecific metaplastic effect, may serve to reset a system in which learning has gone awry."); *id.* at 474–92 (noting that LSD and psilocybin might be useful in treating alcoholism); Matthew W. Johnson, *Classic Psychedelics in Addiction Treatment: The Case for Psilocybin in Tobacco Smoking Cessation*, 56 CURRENT TOPICS IN BEHAVIORAL NEUROSCI. 213 (2022); Johnson, *supra*, in Grob & Grigsby, *supra* note 1, at 493–94 (noting that a 1973 study found a 12-month abstinence rate from heroin use of 25 percent in the group treated with LSD and only 5 percent in the comparison group); *id.* at 497 (noting that a test group administered a psychedelic showed an abstinence rate of 67

- percent after 12 months and 60 percent after 2.5 years); Terri S. Krebs & Pal-Orjan Johansen, *Lysergic Acid Diethylamide (LSD) for Alcoholism: Meta-Analysis of Randomized Controlled Trials*, 26 J. PSYCHOPHARMACOLOGY 994 (2012); Rayyan Zafar et al., *Psychedelic Therapy in the Treatment of Addiction: The Past, Present and Future*, FRONTIERS IN PSYCHIATRY, June 12, 2023; Benedict Carey, *Johns Hopkins Opens New Center for Psychedelic Research*, N.Y. TIMES, Sept. 9, 2019, <https://www.nytimes.com/2019/09/04/science/psychedelic-drugs-hopkins-depression.html?action=click&module=RelatedLinks&pgtype=Article> (“In a continuing trial, Matthew Johnson, an addiction specialist at Johns Hopkins and a member of the new psychedelic center, is investigating how psilocybin treatment compares to use of a nicotine patch in helping people to quit smoking. So far, in the 39 people who have been in the study for at least six months, the abstinence rate in the psilocybin group is 50 percent, compared to 32 percent using the patch. [¶] ‘The most compelling thing that makes psilocybin different from other addiction drugs is that it’s showing this cross-drug efficacy,’ Dr. Johnson said. ‘It appears to have a similar effect, regardless of what drug the person is addicted to.’”); see Sessa, *supra* note 72, at 21 (“[I]n my work as an addiction psychiatrist I understand how feeble our current treatments are for those patients trapped in a cycle of substance misuse... Even with the best current treatments the rates of relapse of alcohol, cocaine, nicotine and opiate dependence are staggeringly high. If psychedelics can inform our practice of addictions, then this is vital research that needs to happen without delay. [¶] The psychedelic drugs are not a panacea, and are not without their risks. But I truly believe that they represent an extra level of treatment that can be safely harnessed to help people who are unable to make progress with established forms of therapy. And that potential should not be ignored.”). *But see* Rucker, *supra* note 14, at 204 (noting that the benefits of abstinence from treating alcohol abuse with psychedelics was significant at one–three months but was not statistically significant at six months).
117. GRINSPOON & BAKALAR, *supra* note 1, at 215 (“There is no doubt that LSD often produces powerful immediate effects on alcoholics; the question is whether they can be reliably translated into enduring change.”), 221 (“Unfortunately, psychedelic experiences have the same weaknesses as religious conversions. Their authenticity and emotional power are not guarantees against backsliding when the same old frustrations, limitations, and emotional distress have to be faced in everyday life.”). Overcoming past maladaptive behavior patterns and learning productive new ones might be the result of developing new interneuronal connections. *See* Nutt, *supra* note 21, at 147–51; Johnson, *supra*, in Grob & Grigsby, *supra* note 1, at 498 (“Whether the pattern of behavior is the self-administration of tobacco, alcohol, cocaine, opioids, or other drugs, or whether it is the cyclical, self-perpetuating thoughts of self-hatred, inevitable failure, or worry that can come with mood disorders, it may be that psychedelics have the ability to at least temporarily allow one to see outside of those narrow patterns, to recognize the suboptimality of these patterns, and therefore become motivated and learn to adopt more optimal patterns of living.”); White, *supra* note 104, at 51–52 (“A trip might help the brain reorganize thought patterns to find new ways of processing anxiety, depression, or trauma, says Laura Hack, an assistant professor of psychiatry and behavioral sciences who treats veterans with PTSD and depression. [¶] ‘During psychedelic therapy, the idea is that people are in this altered state and may be more able to confront difficult topics,’ Hack says. The ideal outcomes of talk therapy are similar. But therapy alone can’t always do the job. ‘It can be very difficult to think about traumatic memories during therapy,’ Hack says. ‘You relieve the trauma. Drop-out rates for trauma-focused therapies can be as high as 50 percent because it’s so hard.’ With the addition of psychedelic treatment, the patient still remembers the trauma but it no longer induces the same symptoms. ‘Because of the effect of the drug, combined with therapy, the patient feels safer, the pain gets softened, you are able to create new memories,’ Hack says. Sometimes, she adds, the results are nearly instant.”).
118. *See, e.g.*, GRINSPOON & BAKALAR, *supra* note 1, at 224–25 (“The purpose of giving psychedelic drugs to the dying can be expressed in many ways, all of them inadequate. Crudely, one could speak of living the last few weeks or months in a psychedelic afterglow. The central idea might be stated as reconciliation: reconciliation with one’s past, one’s family, one’s human limitations. Granted a new version of the universe and his place in it, the dying person learns that there is no need to cling desperately to the self.... Stanislav Grof and Joan Halifax summarize this and much other research on dying.... They emphasize that, even after the emotional afterglow fades, religious and philosophical insights that remain make death easier to bear.”); Brian T. Anderson, *Psilocybin-Assisted Group Therapy for Demoralized Older Long-Term AIDS Survivor Men—An Open-Label Safety and Feasibility Pilot Study*, 27 CLINICAL MED. 100538 (2020) (“These medications can help people overcome their fear of death, and can help make the process of dying a more meaningful and spiritual experience.”); Anthony P. Bossis, *Utility of Psychedelics in the Treatment of Psychospiritual and Existential Distress in Palliative Care*, in Grob & Grigsby, *supra* note 1, at 441, 441 (“[A] primary focus [of psychedelic research] has been on their therapeutic utility in treating persons suffering the emotional distress associated with a terminal illness. The effects of psychedelic-generated states of consciousness have been demonstrated to markedly reduce depression, anxiety, and existential distress associated with cancer and advanced terminal disease.”); *id.* at 457–65 (describing studies finding improved mental states lasting for up to six months of terminally ill patients who received psilocybin); Grob et al., *supra* note 52; Donald M. Topping, *Making Friends with Cancer and Ayahuasca*, in HALLUCINOGENS: A READER 138–55 (Charles S. Grob ed. 2002)(a personal account of taking the latter when afflicted with the former).
119. *See, e.g.*, PASSIE, *supra* note 44, at 8; *id.* at 195–966 (hypothesizing that psychedelics might increase creativity by “breaking conceptual logjams” or by “a slightly increased production of inner stimuli, which leads to a subtle furthering of the flow of thoughts and fantasies,” which is useful in the creative arts).
120. *See, e.g.*, Grinspoon & Bakalar, *supra* note 1, at 183 (citation omitted) (“Kenneth Keniston once classified drug users, with an implicit emphasis on marijuana and LSD, into three groups: ‘tasters,’ who experiment briefly out of curiosity, ‘seekers,’ who use drugs from time to time to intensify experiences or gain insight, and ‘heads,’ who are committed to drugs as a way of life.... All but a few of the people who have taken LSD belong to the first two groups. Typical reasons for using [psychedelics] are curiosity, boredom, persuasion by friends, desire to prove oneself, intellectual and emotional adventure, sensory pleasure, enhanced awareness, self-exploration, religious and mystical insight, spiritual development. There is no reason to assume that these justifications usually disguise profound emotional disturbances.”); Passie, *supra* note 44, at 156–60 (noting that it is unknown whether low doses of LSD increase overall mental functioning as do caffeine and amphetamines, and could function as a nootropic (*viz.*, a substance that helps the brain to remain mentally fit as people age).

A word about “microdosing”: Some people also make nontherapeutic use of psychedelics, especially in minute doses, to enhance creativity or just to enjoy the ride. See *PASSIE, supra* note 44, at 6 (“Some of these people are searching for creating and money making solutions, report success at low doses of LSD at work. They describe enhanced mental flexibility, more focus, more lateral and unconventional thinking. It appears to fit into their quest to work harder, faster, longer.”). For some test subject reports of microdosing’s claimed benefits, see *id.* at 6 (“Microdosing has helped me come up with some new designs to explore and ways of thinking.”); (“[I]t helps me think more creatively and stay focused. I manage my stress with ease and am able to keep my perspective healthy in a way that I was unable to before.”), 39 (“Microdosing makes me feel more productive and gives me outside-of-the-box thinking”; “It’s like you were playing chess and were able to see a few more steps ahead than normal.”; “It gives me fresh eyes, for programming or figuring out algorithmic stuff.”), 60 (“I have had very positive results from infrequent psilocybin microdosing. I have found fast and relatively long-lasting relief from depression and social anxiety.’. Therapeutic effects were also reported [by users] in pain management, obsessive-compulsive disorder (OCD), PTSD, narcolepsy, and migraines.”); Kirsten Grind & Katherine Bindley, *Magic Mushrooms. LSD. Ketamine. The Drugs that Power Silicon Valley*, WALL ST. J., June 27, 2023, https://www.wsj.com/articles/silicon-valley-microdosing-ketamine-lsd-magic-mushrooms-d381e214?mod=Searchresults_pos12&page=1 (“Some start dabbling with psychedelics in search of mental clarity or to address health issues and end up using the drugs more frequently at Silicon Valley parties or raves, where they have taken a role similar to alcohol at a cocktail party... Executives at venture-capital firm Founders Fund, known for its investments in SpaceX and Facebook, have thrown parties that include psychedelics. [¶] Routine drug use has moved from an after-hours activity squarely into corporate culture, leaving boards and business leaders to wrestle with their responsibilities for a workforce that frequently uses. At the vanguard are tech executives and employees who see psychedelics and similar substances, among them psilocybin, ketamine and LSD, as gateways to business breakthroughs. [¶] Spencer Shulem, CEO of the startup BuildBetter.ai, said he uses LSD about every three months because it increases focus and helps him think more creatively. While working alone after hours, he will sometimes take a low-enough dose where he said no one would know he was on LSD. Other times, he’ll take a larger dose alone and connect with nature on a hike. [¶] Shulem, who lives in New York City, said the high expectations of venture-capital firms and investors in general can lead founders to turn to psychedelics to provide an edge. ‘They don’t want a normal person, a normal company,’ he said. ‘They want something extraordinary. You’re not born extraordinary.’”). The evidence, however, is not entirely one-sided. See *PASSIE, supra* note 44, at 163 (“When it comes to ‘creative thinking’ it might be functional to be somewhat ‘irritated’ in the usual way of mental functioning, which may help to gain ‘new’ or unconventional thoughts, ideas or mental processes. However, usual neuropsychological performance results suggest a decrease in performance. Therefore, skepticism seems to be called for . . . with respect to the reports of ‘better performance’ under low doses of LSD or microdosing. However, whilst microdosing might not irritate the brain as much as with higher doses and not lead to performance deficits, it is unclear if a betterment of performance could be achieved in a reliable way.”), 164 (noting that it is “at least theoretically possible” for microdosing to enhance creativity, but that effect is not certain). So far, there is no clinical proof that microdosing is effective. See *NUTT, supra* note 21, at 237–46.

121. Phan & Terry, *supra* note 33, at 8.

122. *Id.* (“The most common adverse effects include anxiety, dysphoria, fear, confusion, increased blood pressure and heart rate, headache, nausea, fatigue, and dizziness which are typically dose-dependent and regarded as well-tolerated.”); see also *PASSIE, supra* note 44, at 166–67 (listing as physical or psychological effects above-normal fatigue and demand for additional sleep, restlessness, sweating, increases in anxiety and migraines, light sensitivity, “psychological vulnerability,” “strange thoughts,” insomnia following late-in-the-day dosing, and deterioration of the ability to perform demanding mental tasks); Goodwin et al., *supra* note 73, at 1644 (“Adverse events occurred in 66 participants (84%) in the 25-mg group, 56 (75%) in the 10-mg group, and 57 (72%) in the 1-mg group. The most frequent adverse events reported in the 25-mg group with onset on the day of psilocybin administration (day 1) were headache (in 24% of the participants), nausea (in 22%), and dizziness and fatigue (in 6% each)... Adverse events that were rated as severe on day 1 were reported by 4% of the participants in the 25-mg group, 8% of those in the 10-mg group, and 1% of those in the 1-mg group. Just one participant (in the 25-mg group) was treated with adjunctive medication (lorazepam for acute anxiety) on day 1. There were no serious adverse events reported on day 1.”).

123. Phan & Terry, *supra* note 33, at 8 (“Specific adverse effects of illusions (LSD), dissociation and sedation (ketamine), muscle tightening and jaw clenching (MDMA), and emesis (ayahuasca) are more compound specific, and similarly regarded as well-tolerated or essential to the therapeutic effect.”) (endnotes omitted). As of 2019, there was no evidence of LSD itself having caused someone to overdose and die, as can happen with opioids, nor has LSD been proven to be addictive. *PASSIE, supra* note 44, at 136–37. There is evidence that ketamine and MDMA might be addictive, but the risk is much less than for heroin or cocaine. *NUTT, supra* note 21, at 277.

124. See *supra* note 33.

125. See Larkin, *supra* note 81, at 8.

126. See, e.g., Carey, *supra* note 116 (“It raises the caution that the investigation of hallucinogens as treatments may be endangered by grandiose descriptions of their effects and unquestioning acceptance of their value.’ Dr. Guy Goodwin, a professor of psychiatry at Oxford wrote, in a recent commentary in the *Journal of Psychopharmacology*. ‘Timothy Leary was a research psychologist before he decided the whole world should ‘Turn on, tune in, and drop out.’ It is best if some steps are not retraced.”); Chris Hamby, *A Fraught New Frontier in Telehealth: Ketamine*, N.Y. TIMES, Feb. 21, 2023, <https://www.nytimes.com/2023/02/20/us/ketamine-telemedicine.html> (“While proponents of at-home ketamine stress the lack of scientific studies showing that long-term medical use might be harmful, the converse is also true: There are few studies showing that it isn’t. Some urge caution.”); Rachel Nuwer, *A Psychedelic Drug Passes a Big Test for PTSD Treatment*, N.Y. TIMES, Nov. 11, 2021, <https://www.nytimes.com/2021/05/03/health/mdma-approval.html> (“[S]ome mental health experts urged restraint. Allen James Frances, a professor emeritus and the former chair of psychiatry at Duke University, who was not involved in the new study, warned that new treatments ‘are never as wonderful as first they seem.’ [¶] ‘All new treatments in medicine have always had a temporary halo effect by virtue of being new and by promising more than they can possibly deliver,’ Dr. Frances said.”); White, *supra* note 104, at 49.

127. For an excellent summary of the concerns, see Madras, *supra* note 73, at 1708 (footnote omitted): “Are clinical trials of psilocybin for depression of adequate quality? Limitations of recent psilocybin trials include the following: limited power, lack of placebo control or comparisons with approved antidepressants, open-label or crossover design, or short-term duration of monitoring; the compromising of conclusions about efficacy by intensive concurrent psychological support and expectancy bias; awareness of trial-group assignments by participants and observers because of intense hallucinogenic effects; overrepresentation of participants with respect to White race, college education, previous hallucinogenic experiences, use of other substances, or intrigue with spirituality; the exclusion of depressed persons with a risk of suicide; and inadequate screening of participants at risk for transitioning from depression to psychotic disorders.”
128. See, e.g., PASSIE, *supra* note 44, at 58 (noting that “[u]p to now [2019], there are no scientifically valid double-blind and placebo-controlled studies with regard to regular intake of LSD in low doses. The only studies available in respect to long-term daily intake looked for development of tolerance...or investigated treatment of autistic children.... Both kinds of studies used higher doses (100 µg and more), which were taken every day without any gaps,” rather than intermittently as most microdosers do), 155 (“pharmacokinetic and pharmacodynamic data on microdosing have so far [that is, as of 2019] not been established”); Carhart-Harris et al., *supra* note 78, at 620, 623 (authors of a 2016 test-of-concept clinical study acknowledging that there were only 12 patients in the study, they self-selected, 11 of the 12 patients had received some prior psychotherapy, and there was no control group); Lieberman, *supra* note 62, at 1460 (noting that some earlier studies “had methodological limitations (the lack of comparator treatments, functional unblinding, expectancy effects, short follow-up periods, imprecise dosing, and variability in treatment settings)” (footnote omitted); Simonsson et al., *supra* note 41, at 450; *Psychedelic Policy*, *supra* note 106 (“These studies have mostly had small sample sizes. Some worry they might overestimate psychedelics’ benefits—notably of microdosing, a fashionable practice of regularly taking small doses of psychedelics. A study by Imperial College London found that people given placebos and actual microdoses reported equal levels of well-being and happiness.”); Smith & Applebaum, *supra* note 90, at 1; Richard J. Zeifman & Lucas O. Maia, *Methodological Concerns in Psychedelic Research: The Issues of Nonequivalent Psychological Support and Generalizability*, 78 EUROPEAN NEUROPSYCHOPHARMACOLOGY 13, 13 (2024) (“A growing body of clinical trials has presented compelling evidence for psychedelic therapy’s therapeutic potential... including psilocybin therapy for major depressive disorder...and MDMA-assisted psychotherapy for posttraumatic stress disorder.... However, there remain important methodological concerns with psychedelic research that warrant attention. While functional unblinding is a frequently discussed concern...the present manuscript focuses on two additional methodological limitations: (1) potential nonequivalence in *quantity* (frequency and duration) and *quality* of psychological support (or psychotherapy) within psychedelic trials (threats to internal validity) and (2) issues with generalizability due to potential sample selection bias (a threat to external validity).”) (citations omitted; emphasis in original).
129. See Goodwin et al., *supra* note 73, at 1645 (“The current trial was designed to address some limitations of previous pilot studies and trials, including limited power, short-duration crossover design, reliance on single-site recruitment of participants, and interpretation of treatment effects that may be confounded by intensive concurrent psychological therapy.”). Consider this description of that 2022 study: “This was a phase 2 double-blind, dose-finding, parallel-group, randomized clinical trial.... The trial was conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. The trial protocol was approved by independent ethics committees or institutional review boards at each participating site. All the participants provided written informed consent.... Recruitment was conducted through referrals from primary care and specialized psychiatry services, online advertisements, and word of mouth. [¶] The trial was conducted at 22 sites in 10 countries in Europe (the Czech Republic, Denmark, Germany, Ireland, the Netherlands, Portugal, Spain, and the United Kingdom) and North America (Canada and the United States) from March 1, 2019, through September 27, 2021. All but one of the principal investigators was a psychiatrist. Both assisting and lead therapists, whose roles are described below, were recruited as psychologists with at least master’s-level qualifications, psychiatrists, master’s-level practitioners, nurses, diploma-level cognitive behavioral therapists, or doctorate-level mental health specialists. These therapists had experience in adult mental health, addiction, dementia, physical health, child or developmental health, family therapy, or eating disorders and experience with patients having severe psychological distress. The therapist-training program that was expressly prepared for the trial had four components: an online learning platform, in-person training, clinical training, and ongoing individual mentoring and webinars. Therapists were required to complete the first three components of the training program before they could lead sessions independently and to engage in the fourth component to continue their professional development. Therapists in training could act as assisting therapists so that there were always two therapists present on the day of drug administration. All the therapists were unaware of the trial-group assignments, did not collect efficacy assessments, and were discouraged from speculating about doses. [¶] Eligible participants completed a run-in period of 3 to 6 weeks, during which antidepressants and other prohibited medications affecting the central nervous system were tapered and discontinued at least 2 weeks before the baseline visit (the day before psilocybin administration). During this period, the participant met with a therapist at least three times to build trust, receive psychoeducation, and prepare for the psychedelic experience. Participants who continued to meet eligibility criteria were randomly assigned in a 1:1:1 ratio to receive a single dose of psilocybin of 25 mg, 10 mg, or 1 mg (control). Randomization was performed at a central location and stratified according to country and the participant’s previous experience with psilocybin. The administration session (day 1) lasted 6 to 8 hours, with the lead therapist who had prepared the participant for the intervention and an assisting therapist in attendance. A trial psychiatrist was available on site for consultation. Administration rooms were designed to provide a nonclinical, calming atmosphere. During the administration session, participants listened to a specially designed music playlist while wearing eyeshades to help direct attention internally. After at least 6 hours and when the psychedelic effects of the drug had fully dissipated, participants returned home.” *Id.* at 1638–39 (endnote omitted).
130. See, e.g., Carey, *supra* note 116 (“Psychedelic trials cannot be ‘blinded’ in the same way most drug trials are: participants know when they have been dosed, and reports of improvement aren’t yet standardized.”); Grob et al., *supra* note 52, at 77 (“Although we used a within-subject, double blind, placebo-controlled design, the drug order was almost always apparent to subjects and investigators whether the treatment was psilocybin or placebo.”); Sara Reardon, *What’s Next for MDMA in Psychiatry?*, 616 NATURE 428, 429 (2023) (“The intense experiences that come with taking MDMA created a unique problem for regulators. The FDA typically requires at least two double-blind, placebo-controlled studies. But there has typically been

little doubt among participants and therapists about who is receiving the drug. [¶] Without a true placebo control, a trial of a psychiatric drug will almost certainly produce positive results, says Erick Turner, a psychiatrist at Oregon Health & Science University in Portland, who has served on FDA advisory committees. ‘Patients know what they’re getting and believe in it,’ he says. ‘They’re going to be biased by that knowledge.’”); Volkow et al., *supra* note 62, at 979 (“The lack of placebos indistinguishable from the drug is another challenge; participants can usually tell if they have been given a psychedelic vs a placebo. Some propose extremely low doses of the active psychedelic as a placebo.”).

131. FDA PSYCHEDELIC GUIDANCE, *supra* note 95, at 8.

132. *Id.*

133. *Id.*; NUTT, *supra* note 21, at 291.

134. FDA PSYCHEDELIC GUIDANCE, *supra* note 95, at 8; Volkow et al., *supra* note 62, at 979.

135. Reardon, *supra* note 130, at 429 (“[T]he FDA approved a ‘special protocol’ for MAPS. After the treatment sessions, each participant’s symptoms were evaluated by psychologists who did not administer the drug and did not know who was in each group. With this protocol in place, the FDA has agreed to base its decisions on the reported efficacy and not take issue with the study design. Outside advisers to the FDA can still raise concerns, however.”).

136. That is not a new concern. The FDA’s 2019 decision to approve ketamine has been criticized by one researcher on the ground (among others) that there was no evidence that ketamine would not have adverse effects when used on an indefinite basis twice or thrice a week. See MOGHADDAM, *supra* note 33, at 127 (noting that “[m]ost of what we know about ketamine is based on a single exposure” of that drug for anesthesia and analgesia, which is important because “[t]he recommended dosing for esketamine”—one of the isomer (or mirror image) forms of the drug—“as an antidepressant is two to three times weekly for an indefinite period.”), 121–36 (discussing potential adverse effects from long-term illicit ketamine use).

137. See, e.g., Goodwin et al., *supra* note 73, at 1637 (“In this phase 2 trial involving participants with treatment-resistant depression, psilocybin at a single dose of 25 mg, but not 10 mg, reduced depression scores significantly more than a 1-mg dose over a period of 3 weeks but was associated with adverse effects. Larger and longer trials, including comparison with existing treatments, are required to determine the efficacy and safety of psilocybin for this disorder.”).

138. See William R. Smith et al., *Correspondence*, 30 NATURE MEDICINE 17, 17 (2024) (patients with cardiovascular problems should not take psychedelics; quoted *infra* note 210); Dana G. Smith, *Psychedelics Are a Promising Therapy, But They Can Be Dangerous for Some*, N.Y. TIMES, Feb. 10, 2023, <https://www.nytimes.com/2023/02/10/well/mind/psychedelics-therapy-ketamine-mushrooms-risks.html?searchResultPosition=1> [hereafter Dana Smith, *Dangerous Psychedelics*]: “Psychedelics’ emerging legal status also means there is very little research about their physical safety. Experts do know that psilocybin and ketamine raise blood pressure and heart rate, so out of an abundance of caution, people with heart conditions, such as uncontrolled high blood pressure, heart disease and arrhythmias, are advised not to take them. [¶] During carefully monitored clinical trials, where dosage is supervised and patients are screened, the drugs ‘appear to be safe from a cardiac standpoint,’ said Dr. Jeremy Ruskin, a professor of medicine at Massachusetts General Hospital who specializes in cardiology. Whether they are as safe for people who are at high risk in uncontrolled settings is unknown.... Dr. Roth said that the risk of developing valvular problems from doing psychedelics a few times ‘is almost probably zero.’ But he is worried about people who microdose—taking tiny amounts of the drugs—several times a week.” Other potential problems are the risk of triggering an epileptic seizure; a hemorrhage resulting from increased cranial pressure; co-using drugs such as MAO inhibitors; using drugs that could heighten or lengthen ketamine’s effect, such as opioids, muscle relaxants, or benzodiazepines; and addiction caused by repetitive, prolonged use. *Id.*

139. See, e.g., Gregory Barber et al., *A Case of Prolonged Mania, Psychosis, and Severe Depression After Psilocybin Use: Implications of Increased Psychedelic Availability*, 179 AM. J. PSYCHIATRY 892 (2022); Dana Smith, *Dangerous Psychedelics*, *supra* note 138 (“When Dr. Charles Nemeroff first met his patient, the 32-year-old woman had already been to see several psychiatrists. Initially, the woman, whose identity has been concealed to protect her privacy, had experienced paranoid and racing thoughts, insisting there were listening devices in her phone and that people were watching her; she even sold her home in an attempt to get away from them. After being given antipsychotic drugs, her mania and psychosis abated, but they were replaced by debilitating depression. [¶] ‘By the time she came to me, she said, “I have no feelings whatsoever. I have no mood variation. I am completely empty,”’ said Dr. Nemeroff, who is chair of the department of psychiatry and behavioral sciences at the University of Texas at Austin Dell Medical School. [¶] While the woman had been treated for mild depression for over 10 years, she’d previously maintained a rich social life and fulfilling career. This—the psychosis followed by the deep depression—was something completely different. And it was triggered by her use of psychedelics. [¶] Eight months earlier, the woman had tried hallucinogenic mushrooms for the first time with friends and had such a great time that she took them again the next day. The second time, though, something went terribly wrong. [¶] ‘She had a full blown psychotic episode for the first time in her life,’ said Dr. Nemeroff, who published the woman’s story as a case report in *The American Journal of Psychiatry* in December. ‘Her friends, who took the same drugs she did both days, had no lasting ill effects.’”) (citing Barber et al., *supra*); *id.* (“When it comes to significant side effects, experts’ primary worry about ketamine, psilocybin and other hallucinogens, like LSD or ayahuasca, is that they can trigger a psychotic or manic episode. Because these drugs (with the exception of ketamine) are not approved for use by the Food and Drug Administration, the safety data on them is scarce. Instead, most of the basis for this concern stems from anecdotal evidence. [¶] What little data does exist suggests that the chances of psychosis developing in the general population is low. One survey of over 1,000 self-reporting recreational psychedelic users did not find a link between drug use and schizophrenia-like symptoms. Another study similarly showed no connection between past psychedelic use and current psychosis or other psychiatric disorders. [¶] However, experts say the risk of psychedelics triggering a psychotic or manic episode is likely elevated for people who have a personal or family history of schizophrenia or bipolar disorder. Consequently, people with these histories are excluded from psilocybin clinical trials and treatment at ketamine clinics. [¶] ‘I had many patients that would give me the story that they were more or less fine, they took LSD, and they’ve had schizophrenia since,’ said Dr. Bryan Roth, a pharmacology professor at the University of North Carolina at Chapel Hill. ‘My guess is they had some underlying predisposition to schizophrenia[,] and it sort of tipped them over the edge.’”).

140. Phan & Terry, *supra* note 33, at 8 (“Acute and chronic psychosis is an adverse effect of particular concern, as exemplified in the case study reviewed above. A systematic review...including psychedelic-assisted therapy studies from 1999 to 2008 noted that among participants receiving psilocybin, 27% experienced fear and 17% paranoia. In other studies, 7% of subjects in the highest dose conditions fit the criteria for acute psychotic reactions. These events were confined to the acute phase and were managed by interpersonal support. Prolonged adverse effects of hallucinogen use such as psychosis and depression are found to be ‘exceedingly rare’ in experimental settings. In another review, no incidences of prolonged psychotic reactions or precipitations or schizophrenia spectrum disorders were identified out of 110 subjects. However, one experienced symptoms of emotional instability, anxiety, and depression which lasted for several weeks. A few subjects described mood swings, “excessive pensiveness and introversion” and memory/concentration issues after the drug session, which generally resolved after a few weeks.... The risk of HPPD [viz., hallucination-persisting perception disorder], as illustrated in the case report, is considered rare and the incidence incompletely known. While the use of psychedelics at therapeutic doses in supportive environments decreases the risk for acute or prolonged psychosis, the added vulnerability for psychosis in those with chronic cannabis use should add a layer of caution.”) (endnote omitted).
- NB: According to the DIAGNOSTIC AND STATISTICAL MANUAL IV-R, HPPD is “a post-hallucinogen intoxication disorder encompassing a range of mostly visual perceptual disturbances that occur within a certain time frame after cessation of drug use.” Leo Hermle et al., *Hallucinogen-Persisting Perception Disorder*, 2 THERAPEUTIC ADVANCES IN PSYCHOPHARMACOLOGY 199, 202 (2012); see also Martinotti et al., *supra* note 87, at 48 (defining HPPD as “a rare, and therefore, poorly understood aspect of hallucinogen consumption: the total or partial recurrence of perceptual disturbances that appeared during previous hallucinogenic ‘trips’ or intoxications and re-emerged without recent use”—more popularly known as a “flashback.”) There are two varieties of HPPD. Type I is benign. “The impairment is mild and the prognosis is usually good. Some of the patients do not report being annoyed by these phenomena: they may indeed consider them as ‘free trips’ resembling psychedelic experiences without consuming a psychoactive substance.” Martinotti et al., *supra* note 87, at 48. Type II, however, “is severe and the prognosis is worse. Some of the patients fail to adapt and live with these long-lasting recurrent ‘trips’, and a consistent fraction needs to be constantly treated.” *Id.* (endnotes omitted). “A vast list of psychoactive substances has been identified and linked with the development of this condition,” including psilocybin, mescaline, LSD, and MDMA, all of which are under investigation for treatment use. *Id.*
141. Reynolds, *supra* note 28, at 477 (finding a need “to remind clinicians and consumers that panaceas for depression do not exist”).
142. “Although current psychedelic development programs are exploring single-dose or intermittent dose treatment paradigms, most of the conditions being studied to date in these programs are chronic. Nonclinical studies to support chronic or chronic-intermittent dosing should be provided if the treatment is not durable and repeat dosing is expected. Sponsors should determine the most appropriate dosing paradigm (e.g., dosing intervals) for each animal species in the repeat-dose toxicity to support their intended clinical studies. The number and types of nonclinical studies to support approval of a marketing application will depend largely on treatment paradigm.” FDA PSYCHEDELIC GUIDANCE, *supra* note 95, at 4 (footnote omitted); see also Coccaro, *supra* note 74, at 980 (noting that “ketamine...ha[s] been found to bring about a rapid reduction in depressive symptoms, often within 24 hours, in some patients with treatment-resistant major depressive disorder, but repeated administration is necessary for a sustained antidepressant effect”) (endnote omitted); Robert Freedman, *Ketamine and ECT in Depression—Risks and Rewards*, 388 NEW ENG. J. MED. 2389, 2390 (2023) (noting that “the results of this current trial suggest that the 3-week treatment was not life-changing. Ketamine treatment was effective, but by 6 months, a brief period in a lifetime of depression, the quality of life was no better with the agent than with [Electro-Convulsive Therapy].”); Sanacora, *supra* note 33, at 399 (noting that there is “compelling evidence that the antidepressant effects of ketamine infusion are both rapid and robust, albeit transient”) (endnote and punctuation omitted).
143. See Nutt, *supra* note 21, at 266–67 (“Taken as a whole the evidence suggests that MDMA may not be suitable as a medicine that’s taken regularly, for example, daily, as SSRIs are. However, when given a limited number of times as part of therapy, where the dose is carefully titrated and people aren’t taking other drugs, the evidence shows MDMA is safe.”). Nutt did not include the word “illicit” in his discussion, but it could be implied by the entirety of what he wrote. By contrast, Professor Andrew Parrott appears to conclude that long-term use of MDMA causes adverse results even when someone does not use illicit drugs. See Andrew C. Parrott, *Clinical and Medical Management of Conditions Caused by MDMA or “Ecstasy,”* in HANDBOOK OF NOVEL PSYCHOACTIVE SUBSTANCES 266, 268 (“The chronic or repeated use of MDMA causes a range of neuropsychobiological problems.”), 268–77 & Tbl. 15.2 (describing those problems), 278 (noting that “[i]n relation to therapy, I am not aware of any study that has specifically investigated MDMA users,” but also noting that “it is well established that the incidence of problems increases with greater lifetime [MDMA] usage”). It is unclear to what extent the drugs Parrott discusses were manufactured illicitly, which matters: There is no quality control for such drugs. Complicating the matter is that the Parrott article predates the two studies by Jennifer M. Mitchell et al. attesting to the benefits of MDMA treatment for PTSD; the Nutt book was published after the second study but might have been in the publication process beforehand.
144. Mitchell et al., *MDMA and Severe PTSD*, *supra* note 23, at 1031 (“[T]his report describes the findings of a short-term pre-specified primary outcome, 2 months after the last experimental session and 5 weeks since the final integrative therapy session; long-term follow-up data from this controlled trial will be collected to assess durability of treatment.”); see Mitchell et al., *MDMA and Moderate-to-Severe PTSD*, *supra* note 82, at 2477 (“In this confirmatory phase 3 study of participants with moderate to severe PTSD, MDMA-AT significantly improved PTSD symptoms and functional impairment, as assessed by CAPS-5 and SDS, respectively, compared to placebo over 18 weeks.”).
145. See *supra* note 111.
146. See, e.g., GRINSPOON & BAKALAR, *supra* note 1, at 179–82 (describing studies suggesting that psychedelics might precipitate the earlier onset of psychosis that would otherwise have occurred later); PASSIE, *supra* note 44, at 165 (“In general studies with LSD and psilocybin have demonstrated that these substances are physiologically very safe if taken only occasionally. However, it remains unknown [in 2019] what effects frequent microdosing has on the human organism.”) (emphasis in original), 169–70 (“Some adverse consequences might result from a daily or every-few-days dosing regimen.

Despite the vast spectrum of studies in the past, we do not know much about any potential long-term changes in the hardware of the human organism that may result from long-term regular LSD use. Professor Nichols said this: 'Using these drugs once a month is one thing. Using them every day, I'm not sure that they are innocuous. They may bring about subtle behavioral and hormonal changes that we don't yet fully understand' [...] (citation omitted), 205 ("Not much is known about the long-term effects of repeated dosing of mescaline on a daily basis."); Bravo, *supra*, in Grob & Grigsby, *supra* note 1, at 337 ("Longer-term side effects of patients using ketamine under medical supervision remain unknown and mostly unstudied, mainly due to the fact that most controlled studies have not had long-term follow-ups or did not measure long-term adverse effects.... However, there is evidence of potential adverse long-term effects gathered from heavy recreational and addicted users of ketamine, as well as patients taking ketamine for pain syndromes. The dose and frequency of ketamine use in addicted patients is much higher than is used to treat psychiatric illness. The adverse effects seen with these heavy users are significant urological pathology, hepatotoxicity, and cognitive deficits.") (citation omitted); cf. Larkin, *supra* note 81, at 11 (discussing studies reaching the same conclusion about cannabis use; "Dr. Volkow's point is that we should be concerned about the risk that cannabis will accelerate the development of mental illness in people who, unfortunately, are already on that sad trajectory or use high-potency THC products for an extended period.").

147. See FDA PSYCHEDELIC GUIDANCE, *supra* note 95, at 4–5 ("Because psychedelic drugs have serotonin (5-HT) activity, a thorough evaluation of binding to 5-HT receptor subtypes should be conducted. Binding to the 5-HT_{2B} receptor subtype has been linked to heart valvulopathy in humans; therefore, sponsors should assess functional activity at the 5-HT_{2B} receptor subtype. If a psychedelic drug is shown to be an agonist at 5-HT_{2B} receptors, a thorough microscopic evaluation of the heart should be conducted to assess for potential heart valve thickening in both rodent and nonrodent repeat-dose toxicity studies, including sectioning of all heart valves.... Long-term exposure to 5-HT_{2B} agonists may induce cardiac valve stiffening. Currently, FDA recommends that sponsors exclude subjects with preexisting valvulopathy or pulmonary hypertension from multiple-dose studies of drugs with this mechanism until this risk can be better characterized."); Nutt, *supra* note 21, at 288; Mason Marks & I. Glenn Cohen, *How Should the FDA Evaluate Psychedelic Medicine?*, 389 NEW ENG. J. MED. 1733, 1733 (2023) (noting "a potential risk of valvular disease, which has been observed with drugs having a high affinity for serotonin 5-hydroxy-tryptamine 2B (5-HT_{2B}) receptors and hypothesized for classic psychedelics such as psilocybin and LSD"). See generally Chandikumar S. Elangbam, *Drug-induced Valvulopathy: An Update*, 38 TOXICOLOGIC PATHOLOGY 837, 837 (2010) ("Normal semilunar (i.e., aortic and pulmonary) and atrioventricular (i.e., mitral and tricuspid) heart valves play an important role in maintaining unidirectional blood flow through the cardiac chambers of the heart, and this function requires not only structural integrity, but also coordinated interactions among several critical valvular components (i.e., for aortic and pulmonary valves, cusps/leaflets, commissures, and their respective supporting structures [roots]; and for mitral and tricuspid valves, leaflets, commissures, annulus, chordae tendineae, papillary muscles, and atrial and ventricular myocardium.").
148. See, e.g., Nutt, *supra* note 21, at 288 (noting that exclusions are appropriate for people diagnosed with psychosis (or who have a close family member with that diagnosis) or bipolar disorder, and patients with a heart condition); Grob et al., *supra* note 52, at 72 (noting that people with a "lifetime history of schizophrenia, bipolar disease, other psychotic illness, and anxiety or affective disorders within 1 year prior to the onset of cancer" were excluded from a study investigating the potential utility of psilocybin treatment to relieve anxiety in end-stage cancer patients); Carhart-Harris, *supra* note 90, at 1408–09 (noting that the clinical study discussed in that article excluded "patients with preexisting psychiatric conditions believed to be incompatible with the limited psychological support that could be made available within the trial"); Nutt & Carhart-Harris, *supra* note 71, at 121 ("Currently, people with a personal or family history of psychosis and bipolar disorder are excluded, as are those with significant health issues ([e.g.,] hypertension) because psychedelics transiently increase blood pressure."); Dana Smith, *Dangerous Psychedelics*, *supra* note 138 ("What little data does exist suggests that the chances of psychosis developing in the general population is low. One survey of over 1,000 self-reporting recreational psychedelic users did not find a link between drug use and schizophrenia-like symptoms. Another study similarly showed no connection between past psychedelic use and current psychosis or other psychiatric disorders. [¶] However, experts say the risk of psychedelics triggering a psychotic or manic episode is likely elevated for people who have a personal or family history of schizophrenia or bipolar disorder. Consequently, people with these histories are excluded from psilocybin clinical trials and treatment at ketamine clinics. [¶] 'I had many patients that would give me the story that they were more or less fine, they took LSD, and they've had schizophrenia since,' said Dr. Bryan Roth, a pharmacology professor at the University of North Carolina at Chapel Hill. 'My guess is they had some underlying predisposition to schizophrenia and it sort of tipped them over the edge.' [¶] Dr. Nemeroff agreed: 'I think the issue with these very powerful medications is that there are probably people who are genetically vulnerable to a major psychiatric illness, but they haven't reached the threshold yet. And then what these medications might do is unleash it.' [¶] Backing up these concerns, one of the few studies looking at psychedelic use in people with bipolar disorder found that one-third reported that their symptoms worsened after taking psilocybin recreationally, and 3 percent had to seek emergency medical care. [¶] As a result, Dr. Roth said, 'Anybody with a serious psychiatric disorder—like schizophrenia, bipolar disorder—should not take psychedelics.'"); *supra* note 138.
149. See Bravo, *supra*, in Grob & Grigsby, *supra* note 1, at 338–39 ("There are multiple unanswered questions about the psychiatric use of ketamine, including how best to optimize set, setting, dose, route, frequency, and the role of adjunctive psychotherapy. What patient characteristics and diagnostic entities respond best to ketamine? What are the possible long-term adverse effects of ketamine therapy? The role of [ketamine-assisted psychotherapy], inspired by psychedelic models of healing, shows promise, but much remains to be investigated. Are psychoactive effects important in Ketamine's efficacy, or just side effects to be avoided?").
150. See Schindler, *supra* note 113, at 519 ("[P]sychotic and manic disorders are exclusionary to the studies, as are cardiac conduction defects, hormonal imbalances, and other conditions that may place subjects at risk."); White, *supra* note 104, at 53 ("[Boris] Heifets [assistant professor of anesthesiology and psychedelics researcher at the Stanford Center for Precision Mental Health and Wellness] sees 'a lot of opportunity for real good coming from these compounds, but there's also a whole lot of collateral to avoid,' he says. In trial, participants are screened for a personal or family history of psychotic disorders, and a therapist or other support person establishes a rapport with them. 'Rushing the drugs to market before safety guidelines are in place opens up the possibility of risks that currently are controlled under scientific settings.'").

151. See *supra* note 27.
152. See McClure-Begley & Roth, *supra* note 27, at 470 (“In summary, evidence for the therapeutic effects of psychedelic compounds is mounting, at least under specific clinical settings and for select demographics of people with certain conditions. For the classical psychedelics gaining interest in the clinical domain, studies examining longer-term durability of therapeutic benefits and more comprehensive assessments of safety margins, particularly involving patient populations presenting with multiple comorbidities, will be highly valuable. Additional research and development is also required in the basic science domain to increase our understanding of the underlying mechanisms, and to diversify the chemical space of drugs that act via these mechanisms so that we may be able to benefit the greatest proportion of the affected population.”).
153. “The initial FDA approval of ketamine was for its sole use as an anesthetic. Safety assessments of anesthetic drugs are generally limited to determining the lethal dose and potential side effects after exposure to a single dose of the drug. Thus, the initial approval of ketamine did not include any safety information about its effect after repeated use. The clinical off-label use of ketamine (i.e., its use for purposes other than the FDA-approved use as an anesthetic) prior to antidepressant use also involved single or infrequent dosing. This involved the use of ketamine to model psychosis in healthy volunteers or for pain relief. We know virtually nothing about the long-term consequences of indefinite two or three times per week dosing of ketamine or esketamine in humans.” MOGHADDAM, *supra* note 33, at 128.
154. Volkow et al., *supra* note 62, at 979; see Loder, *supra* note 44 (“It is probably not necessary to cause hallucinations to create the sort of neuronal plasticity that is increasingly thought to be important in the treatment of brain disorders. One theory is that many psychiatric and neurodegenerative conditions are a result of ‘cortical atrophy’, the loss of connectivity between the connections of neurons in the pre-frontal cortex. Psychedelics seem to allow these connections to be strengthened and reconnected.”).
155. See Bravo, *supra*, in Grob & Grigsby, *supra* note 1, at 338–39 (quoted *supra* note 149); McClure-Begley & Roth, *supra* note 27, at 470–71 (“It is currently unknown whether the subjective experience of a psychedelic drug is a necessary component of its ability to produce therapeutic benefit.... Knowing what we do about the diverse constellation of signalling processes engaged by the 5-HT_{2A} receptor, and others implicated in the myriad effects of psychedelics, it is possible that a drug binding the receptor(s), but with different agonist activities and/or polypharmacology to psilocin, will have substantially different effects.... In this regard, a new paper suggested that the psychedelic actions of psilocybin in mice could be blocked without affecting its antidepressant drug-like actions. Here the authors show that pretreatment with the 5-HT_{2A} receptor antagonist ketanserin attenuates, but does not abolish, psilocybin’s HTR [head twitch response] in mice without affecting psilocybin’s antidepressant drug actions in two animal models. Although these findings are intriguing, given the non-translational value of many rodent models of antidepressant drug actions, and the substantial polypharmacology inherent with classical psychedelics, further investigation is warranted.”) (endnote omitted).
156. Volkow et al., *supra* note 62, at 979 (footnotes omitted); compare David B. Yaden, *The Subjective Effects of Psychedelics Are Necessary for Their Enduring Effects*, 4 AM. CHEMICAL SOC’Y PHARMACOLOGY & TRANSLATIONAL SCI. 568, 570 (2021) (“Based on studies of experimental studies of moderate to high dose psychedelics we believe that the case for subjective effects playing a major role in enduring beneficial effects is compelling.”), with David E. Olson, *The Subjective Effects of Psychedelics May Not Be Necessary for Their Enduring Effects*, 4 AM. CHEMICAL SOC’Y PHARMACOLOGY & TRANSLATIONAL SCI. 563, 565 (2021) (“While preliminary evidence suggests that the subjective effects of psychedelics are not *necessary* to produce therapeutic responses, they may be critical for achieving *maximal* efficacy.”) (emphasis in original).
157. FDA PSYCHEDELIC GUIDANCE, *supra* note 95, at 6.
158. *Id.* at 7 (citing U.S. FOOD & DRUG ADMIN., CNTR. FOR DRUG EVALUATION & RESEARCH RSCH.(CDER), ASSESSMENT OF ABUSE POTENTIAL OF DRUGS: GUIDANCE FOR INDUSTRY (2017)). The FDA has also noted, however, that “a human abuse potential study may not be scientifically necessary for certain psychedelic drugs to support the abuse potential assessment in a new drug application when the subjective effects predictive of abuse are well characterized from extensive clinical studies and robust epidemiological data exist to demonstrate that individuals are using the psychedelic drug for abuse purposes.” *Id.* Now that the Grateful Dead has ceased touring, it is unclear whether drug sponsors still have “robust epidemiological data” freely available.
159. Volkow et al., *supra* note 62, at 979.
160. The problem is a particularly acute one in connection with the need to obtain informed consent. Some commentators have noted the difficulty of adequately describing the psychedelic experience to someone who has never experienced it beforehand and the need to advise patients that the tap cannot be turned off if the experience is a painful one. See Smith & Applebaum, *supra* note 90, at 1–2 (citations omitted): “Psychedelic-specific issues in informed consent stem from at least four sources. First, though not yet fully understood, classical psychedelics appear to create changes in mental states that are qualitatively and quantitatively different than those created by most psychotropic medications. They are often characterized as ‘ineffable experiences,’ such as ‘oceanic boundlessness,’ ‘dissolution of the ego,’ and ‘shifts in values or personality,’ and often produce feelings of deepened spirituality or ‘connectedness’ with other individuals, animals, or nature.... The difficulty of conveying these experiences to people naïve to psychedelics is a challenge for a meaningful consent process, since the words and concepts will be unfamiliar to many people. Indeed, for anyone to imagine what they would be like if their values changed or their awareness was altered is a daunting task. Yet, decisions about whether to engage in psychedelic treatment may be affected by a person’s openness to these experiences and willingness to embrace the changes that may occur, underscoring the importance of attempting to convey them clearly.... [¶] Second, the altered states of consciousness induced by both classical psychedelics and related agents, like MDMA, may provoke acutely dysphoric states marked by disorientation, anxiety, paranoia, and altered sensory experiences (i.e., ‘bad trips’). In the midst of such states, research participants and patients may change their minds about the risk-benefit ratio of participation.... However, once begun, there are challenges in aborting or reversing the psychedelic experience. For instance, while clinicians may attempt to mitigate its most disturbing effects, through redirection and calming procedures or even administration of antipsychotic medications, the effects may persist, and some find involuntary antipsychotic injections traumatizing. Hence, the nature of the decision to engage in psychedelic

therapy, which is for practical purposes irreversible, along with the possibility of an adverse response, needs to be very clear to participants and patients when consent is obtained. [¶] Third, given the current media environment, which has tended to exaggerate the proven benefits of psychedelic therapy, many participants may bring heightened and unrealistic expectations to the consent process—what one team of psychedelic researchers has described as reflecting the ‘uncanny allure’ of the drugs.... Contributing to these expectations is the reality that many potential beneficiaries of psychedelic medicine are suffering from chronic, painful and intractable conditions, such as treatment-resistant depression (TRD). Unrealistic expectations need to be monitored actively and addressed in the consent process, both out of fairness to the person about to undergo psychedelic treatment and to avoid backlash against psychedelic research and treatment when such expectations are not met. [¶] Finally, in the informed consent process, it is critical to attend to potential longer-term consequences of psychedelic treatment, including re-exposure to trauma, existential distress, and later flashbacks to the psychedelic experience, as well as destabilization of underlying psychotic or manic illness.”

161. See Gavin P. Schmitz & Bryan L. Roth, *G Protein-Coupled Receptors as Targets for Transformative Neuropsychiatric Therapeutics*, 325 *AM. J. PHYSIOL. CELL PHYSIOL.* C17 (2023).
162. See, e.g., Sarah McNamee et al., Viewpoint, *Studying Harms Is Key to Improving Psychedelic-Assisted Therapy—Participants Call for Changes to Research Landscape*, 80 *JAMA PSYCHIATRY* 411, 411 (2023) (“Psychedelic-assisted therapy combines 2 psychoactive components: drugs and psychotherapy. This innovative combination is theorized to create a synergy that enhances the effects of each component[.]”); David B. Yaden et al., *Preparing for the Bursting of the Psychedelic Hype Bubble*, 79 *JAMA PSYCHIATRY* 943, 943 (2022) (“Jung’s technique of reaching the collective unconscious was through active imagination, involving intentional engagement with images and symbols that emerge from dreams and fantasies. However, the LSD experience is an induced, passive experience, with judgment suspended while imagery is triggered involuntarily by the drug. Grof concluded that because the experience was drug induced, it is the psychotherapeutic integration of the experience that is therapeutic. Richards confirmed that, writing ‘the benefits of a well-planned psychedelic experience come not from the substance itself but rather from the integration of enduring memories of the particular states of consciousness that were experienced during the period of drug action. That is why those who encounter profound states of mind typically express little interest in repetitive ingestions in the near future.’... Lessons learned from those years remain pertinent today. First and foremost, this is a drug-assisted psychotherapy. Psychedelic drugs are not a specific drug treatment for any psychiatric disorder or addiction, but rather facilitate treatment for them with appropriate psychotherapy. The drug effects are not predictable and are contingent on psychological state, set, and setting and dependent on dose. Psychotherapy is essential to integrate experiences arising during these typically 5-hour to 6-hour music-assisted sessions.”) (endnote omitted).
163. Nuwer, *supra* note 126; see also Nutt, *supra* note 21, at 124 (“In the U.S., ketamine is now prescribed both with and without therapy. There are no head-to-head studies comparing the use of ketamine in depression with and without therapy. But the University of Exeter KARE study with alcohol-dependent people...found ketamine plus psychotherapy was better than ketamine without therapy.”).
164. Sessa, *supra* note 72, at 28.
165. Grinspoon & Bakalar, *supra* note 1, at 158.
166. “Psychedelic medicines carry a truly uncanny allure and risk-benefit profile, and regulatory risk evaluation mitigation strategies can have their shortcomings. Hence, our collective challenge as future psychedelic providers is to develop a system of rigorous peer-review and supervision that will allow professionals in the field to more safely navigate the possible, and at times unavoidable, ethically murky undercurrents that might emerge.” Brian T. Anderson et al., *Psychedelic Medicine: Safety and Ethical Concerns*, 7 *LANCET PSYCHIATRY* 829, 829 (2020) (footnote omitted); see also Passie, *supra* note 44, at 138 (noting that “some methodologically sound studies” found “positive psychological consequences” of taking LSD or psilocybin but adding that “serious damage can result from ingestion of LSD in uncontrolled circumstances or by vulnerable individuals”); Reardon, *supra* note 130, at 429 (“In trials, the drug is administered by a pair of MAPS-trained therapists who guide the participant’s experience through scripted sessions that also allow for improvisation. The FDA does not regulate the guided-therapy component, only the drug—but [MAPS founder and president Rick] Doblin says that the two are inseparable. ‘What we believe is that the results that we got were not from MDMA,’ Doblin says. ‘They were from highly trained therapists who are then using MDMA.’”).
167. Sessa, *supra* note 72, at 27.
168. See Smith, *Good Psychedelic Therapy*, *supra* note 108 (“Before you take the drug, the clinician should meet with you for several hours over a few days to explain what the treatment will entail, especially regarding the drug’s physical and psychological effects. The therapist should ask about your history and symptoms, as well as your goals and intentions for the treatment. [¶] The therapist might advise you to adopt a certain frame of mind during the session or teach you breathing or meditation techniques to use if you are faced with an uncomfortable emotion or physical sensation while on the drug.... For most of a drug session with MDMA or psilocybin, the patient is typically lying down, eyes closed, listening to music. The experience generally does not involve much talking and is more internal for the patient. [¶] If the patient starts to feel anxious or is encountering a traumatic memory or vision, the therapist might offer reassurance or guidance through a breathing exercise. In those instances, the goal is not for the patient to avoid or be distracted from the experience. ‘The therapist role here is to try to help people stay with it,’ Dr. Raison said. ‘If you fight the experience, you tend to have bad outcomes.’... The integration sessions, when the patient processes the experience in the days and weeks after the trip, look the most like traditional therapy. The exact number of sessions varies, but four hours spread over two or three weeks is typical, though some experts say that isn’t long enough. [¶] The therapist helps the patient try to make sense of the feelings, insights and memories that emerged while on the psychedelic. The most common tactic, Dr. Raison said, is to ask open-ended questions and let the patient guide the conversation. [¶] Some researchers are starting to experiment with alternative therapeutic approaches, such as cognitive behavioral therapy or acceptance and commitment therapy, that encourage patients to re-examine beliefs about themselves, potentially aided by insights made during the psychedelic session. [¶] To Dr.

Lehrner, what researchers should be working to standardize now are general therapeutic principles while they continue testing whether the treatment as a whole is safe and effective. ‘Afterwards,’ she said, ‘people may investigate: “Well, what if we tweak it like this? What if we change it like that?”’ [¶] Ms. McNamee disagreed. ‘I worry about how the field might be moving too quickly,’ without sufficient research into what constitutes safe and ethical practice, she said. ‘That we may standardize things that are problematic, I think, is something that’s worth thinking about.’”)

169. See Luana Colloca et al., *The Intricate Interaction Between Expectations and Therapeutic Outcomes of Psychedelic Agents*, 80 JAMA PSYCHIATRY 867, 867 (2023).
170. Smith, *Good Psychedelic Therapy*, *supra* note 108.
171. McNamee et al., *supra* note 162, at 411 (“We outline 2 concerns regarding the psychotherapy component: (1) the lack of empirical evidence for the quality and safety of the psychological support provided during dosing sessions, and (2) the interactions between the drug effects and the psychotherapy. [¶] In the absence of empirically derived and tested psychotherapy practices during dosing sessions, psychedelic therapists follow a set of untested guiding principles based on observations and beliefs from early psychedelic researchers.”); 412 (“We point to the psychotherapy protocols that accompany psychedelic administration as an understudied and undertheorized source of preventable risk in PAT.”); Smith, *Good Psychedelic Therapy*, *supra* note 108 (quoting Dr. Charles Raison, director of clinical and translational research at the Usona Institute in Wisconsin and a professor of psychiatry at the University of Wisconsin, and Sarah McNamee, licensed psychotherapist and research coordinator at the McGill University School of Social Work); Roman Palitsky et al., *Importance of Integrating Spiritual, Existential, Religious, and Theological Components in Psychedelic-Assisted Therapies*, 80 JAMA PSYCHIATRY 743, 743 (2023) (“Although there is consensus that psychotherapeutic treatment should accompany psychedelic administration, the nature of the psychotherapy is often omitted from trial reporting, and there is little agreement about the nature, components, and duration for such treatment. To achieve an evidence-based, effective PAT, the psychotherapeutic components of treatment must be clearly specified, rigorously tested, tailored to mediators and moderators of response, and optimized for safety.”) (endnote omitted). A variety of options are used. See Marks & Cohen, *supra* note 147, at 1734 (“Most psychedelics trials provide some form of psychological support during and after drug administration. Clinician monitors who observe participants experiencing acute psychedelic effects typically provide this support using a range of methods. Researchers also provide support during follow-up sessions.”).
172. See Panik & Presti, *supra*, in Grob & Grigsby, *supra* note 1, at 170 (noting that people with cognitive disorders (e.g., psychosis), mood disorders (e.g., bipolar disorder), a potential genetic predisposition to severe mental disorder (e.g., a family history of schizophrenia) might react adversely to psychedelics); Peter Grinspoon, *The Popularity of Microdosing of Psychedelics: What Does the Science Say?*, HARV. HEALTH PUBL’G BLOG, Sept. 19, 2022, <https://www.health.harvard.edu/blog/the-popularity-of-microdosing-of-psychedelics-what-does-the-science-say-202209192819> (“It is important to mention that the use of all psychedelic drugs should be undertaken with utmost caution—if they should be used at all—in patients with major mental illness such as schizophrenia or bipolar disorder. For safety reasons, these patients are typically excluded from studies involving psychedelic drugs.”); Ross et al., *supra* note 29, at 189 (“[G]iven that psilocybin and other classic psychedelics are known to exacerbate psychosis in individuals with psychotic spectrum illnesses, all modern human psychedelic clinical trials at academic medical centers have excluded individuals with psychotic spectrum illness (i.e., schizophrenia, schizoaffective disorder, bipolar I with psychotic features) or those with a known positive family history of psychotic or bipolar I illness...”) (footnote omitted).
173. See, e.g., Goodwin et al., *supra* note 73, at 1639.
174. See Madras, *supra* note 73, at 1708–09 (“Because psilocybin produces unpredictable hallucinogenic effects, administration is necessarily coupled to an extensive, nontraditional psychotherapy program. Sessions of 6 to 8 hours’ duration are conducted in a non-clinical, calming living-room environment, with participants listening to a specially designed music playlist and isolated by eyeshades and earphones to help direct attention internally. Hosted by a lead therapist and an assistant, sessions are preceded by rigorous preparation for the experience and followed by integration discussions. Therapist training is intensive, and requirements for a cadre of qualified therapists may be difficult to achieve.”); Nutt & Carhart-Harris, *supra* note 71, at 121 (“Verbal engagement with the therapists is not expected, and most patients go deep into their own visions, thoughts, and memories and do not want to be disturbed. But the guide or guides are present, and with permission, they can hold the patient’s hand to reassure the person that he or she is being looked after.”); *infra* text accompanying notes 109–11.

Consider this 2016 description of the structure of one research study: “Screening consisted of written informed consent, a thorough evaluation of the patient’s physical and mental health background, a psychiatric interview (Mini-International Neuropsychiatric Interview), clinician assessments of depression severity (the 21-item HAM-D and the Montgomery–Åsberg Depression Rating Scale [MADRS], and Global Assessment of Functioning [GAF]; all assessed by MBo [viz., the lead trial psychiatrist]), and additional patient-rated scales (16-item Quick Inventory of Depressive Symptoms [QIDS], Beck Depression Inventory [BDI—original version], Spielberger’s State-Trait Anxiety Inventory [form 2, trait version only; STAI-T], and the Snaith–Hamilton Pleasure Scale [SHAPS]). Patients also received a thorough physical health check, consisting of an electrocardiogram, routine blood tests, blood pressure, heart rate, and physical examination. At the end of screening, eligible patients were given an opportunity to meet with the two clinical psychiatrists who would support them through the remainder of the trial. [¶] Eligible patients attended a subsequent visit involving a baseline functional MRI (fMRI) scanning session lasting 60 min, followed by an extensive preparatory session with their allocated psychiatrists; fMRI data will be reported elsewhere. This preparatory session involved inviting the patient to talk openly about their personal history (including thoughts on the origins of their depression), a discussion of psilocybin’s psychological effects, and simulation of aspects of the dosing session itself, such as listening to a sample of the session music while wearing eyeshades. The preparatory session typically lasted for 4 h, with lunch and breaks provided. [¶] Patients enrolled in the study attended two subsequent dosing sessions that were separated by 7 days. No more than one patient was dosed on any given day. Patients arrived at the research facility (Imperial Clinical Research Facility) at 0900 h, gave a urine sample for drugs of abuse (including amphetamines, benzodiazepines, opiates, and cannabinoids), performed a breathalyser test for alcohol use, and completed interim QIDS, BDI, and

STAI-T assessments to ensure no substantial deviation from baseline measures. They were then taken to a dosing room that was pre-decorated ([e.g.,] with low lighting). Patients were invited to relax on a ward bed in a supine or reclined position and music was played through high-quality stereo speakers and earphones. The two psychiatrists sat on either side of the bed. Patients were supervised at all times by at least two staff members. [¶] .. Subjective ratings of the acute altered state of consciousness using the revised 11 dimension altered states of consciousness questionnaire (11D ASC) were completed 6–7 h after dosing. [¶] Psychiatrists adopted a non-directive, supportive approach, allowing the patient to experience a mostly uninterrupted inner ‘journey’. Check-ins ([i.e.,] asking the patient how they are feeling) occurred at the same timepoints as the physiological recordings. Tranquilising medications (oral lorazepam and risperidone) were available if necessary.” Carhart-Harris, *supra* note 78, at 621–22; *see also*, e.g., Smith, *Good Psychedelic Therapy*, *supra* note 108 (quoted *supra* note 171).

175. Grob & Grigsby, *supra* note 1, at xii.

176. Zeifman & Maia, *supra* note 128, at 13 (“Psychedelic therapy involves the administration of a pharmacological agent alongside psychological support. To establish the efficacy of a pharmacological agent within placebo-controlled trials, it is essential that the *quantity* and *quality* of the psychological support provided are equivalent across conditions. Although psychedelic trials initially assign participants an equivalent quantity of psychological support, several elements may contribute to individuals in the active condition receiving more psychological support.... Given the psychoactive, emotionally evocative, and sometimes psychologically destabilizing effects of psychedelics, individuals who are administered a psychedelic may receive more psychological support through additional sessions, extended contact on dosing days, and longer check-ins. If this is the case, between-group differences may be attributable to the quantity of psychological support participants receive, rather than the psychedelic substance itself. It is therefore problematic that psychedelic trials generally do not report on the exact frequency or duration of psychological support in each condition, and fail to control for these potential confounds. [¶] There is also lack of clarity as to whether the quality of the therapy provided across treatment conditions in psychedelic trials is equivalent. Within psychotherapy research, measurements of therapist competence (i.e., level of skill shown by the therapist) and adherence (i.e., following a therapy manual) are important for ensuring that the quality of the intervention is equivalent across treatment groups.... It is therefore problematic that some psychedelic trials do not describe monitoring adherence and that no trials have reported on adherence or competence ratings nor controlled for differences in these ratings across treatment conditions. Additionally, only one psychedelic trial evaluated therapeutic alliance...a critical element across therapeutic interventions. [¶] These potential imbalances in the quantity and quality of psychological support may be especially exacerbated within psychedelic trials due to unblinding of therapists and investigators.”) (citations omitted; emphasis in original).

Writing in the *Journal of the American Medical Association Psychiatry*, Dr. Charles F. Reynolds III listed a few important questions to be answered: “The first of these questions has to do with the expectancy effects associated with the extensive psychotherapeutic support and education provided to participants before, during, and after their exposure to psilocybin. Face-to-face time reportedly totaled some 13 hours, a total that is not considerably different from the 16 to 20 hours of face-to-face time in complicated grief therapy. Interestingly, in the case of prolonged grief disorder, exposure to concurrent citalopram or pill placebo did not affect the overall high rates of efficacy of complicated grief psychotherapy, as reported by [M. Katherine Shear et al., *Optimizing Treatment of Complicated Grief: A Randomized Clinical Trial*, 73 *JAMA PSYCHIATRY* 685 (2016)]. Here is a question: would a double-blind experimental design, entailing the use of pill placebo, or an active comparator with psychotropic effects ([e.g.,] an anxiolytic or an antidepressant), in a model of medication-assisted psychotherapy, yield results that are comparable with those reported by Davis et al. in their single-blind, immediate vs delayed exposure to psilocybin paradigm? A second set of questions highlights the need to know for whom psychedelic-assisted psychotherapy is appropriate (or not), particularly in patients with depression who are suicidal or have a history of suicide attempts. Participants in [Davis et al., *supra* note 90] were noteworthy for the general absence or low level of suicide risk. More broadly, however, personalizing the management of depression has to entail an understanding of the multiple contexts in which depression occurs, including genetic, developmental, psychosocial, cultural, medical, neurocognitive, and spiritual (as reflected in a person’s values, what ultimately matters to them, and so on). [¶] Another question may be, what are the patient and environmental characteristics that moderate or alter the variability of response to medication-assisted supportive psychotherapy? A final set of questions relates to the durability and maintenance of antidepressant response, with respect to both symptom burden and major role functioning. How does psychedelic-assisted psychotherapy fit into both acute and long-term care for depressive illness, not only to get patients well but also to keep them well and living lives of meaning and fulfilment?” Reynolds, *supra* note 28, at 477; *see also* Anderson et al., *supra* note 166, at 829 (footnotes omitted) (“We agree that these compounds have the potential to lead to substantial innovations in therapeutics and neuroscience, but believe that they can be disruptive for other reasons. Classic psychedelics, such as psilocybin and lygerside, and atypical psychedelics, such as MDMA, have been found to be relatively well tolerated in early-phase clinical trials. However, psychedelics can have lingering effects that include increased suggestibility and affective instability, as well as altered ego structure, social behaviour, and philosophical worldview. Stated simply, psychedelics can induce a vulnerable state both during and after treatment sessions. Therefore, to assure the safe and responsible clinical administration of psychedelics, we need to develop standards that are commensurate with the novelty and breadth of the effects that these compounds can have on individuals.”); *id.* (“[T]he more pressing issues affecting the roll out of these therapies will arise from dynamics between providers and patients ([e.g.,] the challenges of co-creating truly informed consent, minimizing conflicts of interest, and avoiding practicing outside of the provider’s scope of competency.”).

177. Madras, *supra* note 73, at 1709 (“If legalization and commercialization are allied with the medical movement, psychedelic shops and ‘clinics’ could proliferate even for vulnerable populations, and rigorously designed medical protocols will be compromised. [¶] The United States failed to prevent conflation of biomedical and commercial marijuana enterprises. The pattern should not be repeated with hallucinogens.”); *cf.* Chris Roberts, *Anyone Can Get Their Medicine: California Has Already Pretty Much Legalized Marijuana. And That’s Okay*, *SF WEEKLY* (Sept. 14, 2014), <http://www.sfweekly.com/sanfrancisco/chem-tales-marijuana-legalization-recreational-use/Content?oid=3154256> (“I am often asked how to legally obtain some weed in San Francisco, what ailment is required to get a medical marijuana recommendation. This fascinates people to this day, out-of-towners as well as locals. When I am honest, I say, ‘About \$40 and 10 minutes.’”).

178. See GRINSPOON & BAKALAR, *supra* note 1, at 63 (“The fact that psychedelic visions could be hellish as well as beatific was another fascinating challenge to the user rather than an objection to this astounding new way of feeding metaphysical appetites.”), 157 (citation omitted) (“A voyage like this might be expected to produce some casualties.... [T]he American Psychiatric Association declared in 1966 that ‘the indiscriminate consumption of this hazardous drug can and not infrequently does lead to destructive physiological and personality changes.’”) (citation omitted; quoting Conrad J. Schwartz, *The Complications of LSD: A Review of the Literature*, 146 J. NERVOUS & MENTAL DISEASE 174, 181 (1968)), 186 (“[T]he most likely candidates for adverse reactions are schizoid and prepsychotic personalities with a barely stable ego balance and a great deal of anxiety, who cannot cope with the perceptual changes, body image distortions, and symbolic unconscious material produced by the drug.”); Kevin F. Boehnke et al., *Applying Lessons from Cannabis to the Psychedelic Highway—Buckle Up and Build Infrastructure*, 3 JAMA PUBLIC HEALTH 221618, at 3 (2022) (“Stanislav Grof wrote that the ‘potential significance of...psychedelics for psychiatry and psychology [is] comparable to the value the microscope has for biology or the telescope has for astronomy’.... As with telescopes or microscopes, trained hands and thoughtful, curious minds are essential to realizing the promise of psychedelics. The lessons of cannabis should also remind us that the medical utility of psychedelics is surely limited to specific circumstances, a narrative often forgotten amid pervasive media promotion. Consequently, our goal should be to craft balanced policy that appropriately shapes societal mindset and setting to facilitate safe experiences for people using these medicines, knowing that some will benefit and some will not.”) (citation omitted); Sessa, *supra* note 90, at 201; *supra* notes 146–48 and *infra* notes 178, 193, & accompanying text.
179. See Volkow et al., *supra* note 62, at 979 (noting that “adverse events like suicidal behavior, while rare, have been reported in psilocybin trials”).
180. Kristina Fiore, *If Ketamine Is So Safe, What Happened to Matthew Perry?*, MEDPAGE TODAY, Dec. 19, 2023, <https://www.medpagetoday.com/popmedicine/cultureclinic/107942> (“Smita Das, MD, PhD, MPH, of Stanford University in California and chair of the Council on Addiction Psychiatry at the American Psychiatric Association, noted that clinicians would closely monitor many parameters, such as heart rate and simultaneous medications, when giving ketamine. ‘When that sort of monitoring or supervision isn’t in place, then there are a multitude of different things that can happen with external factors—if there are other medical conditions that aren’t accounted for that might put somebody at risk, or there are other substances involved,’ Das told *MedPage Today*. ‘All these things can contribute to a poor outcome.’”).
181. See Bossis, *supra* note 118, in Grob & Grigsby, *supra* note 1, at 458 (noting that “established guidelines” addressing “set and setting” include interpersonably supporting preparatory sessions, medication session monitoring, and post[-]medication therapeutic integration”); Marks & Cohen, *supra* note 147, at 1734 (noting that “[s]ome stakeholders” deem clinical support “essential to psychedelic treatment” because it “could reduce the risk of serious adverse events, including psychosis, suicidal ideation, and chronic perceptual disturbances.... So far, clinical trials haven’t compared various levels of support or compared psychedelics alone with psychedelics plus support. Most likely, some baseline level of support is advisable, and additional layers may prove beneficial.”).
182. See Smith, *Good Psychedelic Therapy*, *supra* note 108 (“‘I’m really concerned about the ways in which well-meaning therapists can do harm,’ said Sarah McNamee, licensed psychotherapist and research coordinator at the McGill University School of Social Work. [¶] Because people are so emotionally vulnerable while they’re on psychedelics, there is a greater risk for psychological injury, particularly by inept or inexperienced practitioners. ‘It could be easy to make someone worse,’ said Janis Phelps, director of the Center for Psychedelic Therapies and Research at the California Institute of Integral Studies, which offers degrees in psychology and counseling.”); Volkow, *supra* note 62, at 980 (“[S]ince patients are particularly vulnerable during a psychedelic experience due to altered perceptions, an increased posture of openness, and potential for the clinician to be imbued by the patient with medical and spiritual authority, the clinical staff’s role needs to be structured in ways that prevent possible abuses.”).
183. See Boehnke et al., *supra* note 178, at 2 (“[A]s with cannabis, few monitors are trained to skillfully manage psychedelics clinically, highlighting the need for expanded educational opportunities for interested monitors and students. Organizations such as Fluence and the Multidisciplinary Association for Psychedelic Studies have substantial experience offering monitor trainings, largely focused on building skills around drug administration, harm reduction, and psychedelic integration therapies. Efforts are also underway at the Center for Psychedelic Drug Research & Education at The Ohio State University to create the first academically accredited continuing education certificate program and undergraduate minor in psychedelic studies. Such training efforts are vital given that communities, families, and the public will need education to better understand and support loved ones who may seek out psychedelic treatments.”); Nutt & Carhart-Harris, *supra* note 71, at 122 (“Another issue is how to provide enough psychedelic-trained therapists and ensure good practice through structuring, manualizing, monitoring, and delivering quality training and practice. Several of the centers currently researching psychedelic therapy are offering training under the supervision of more experienced therapists; for example, Kings College in London, in the UK, has successfully piloted group training of potential therapists, some of whom also received psilocybin as part of this course (though self-experience is not required). If this form of therapy does become more widely used, more formal training of large numbers of therapists will be required.”). For some suggestions in this regard, see Boehnke et al., *supra* note 178, at 2 (“[T]he extensive time commitments required for monitors to provide this intervention creates an accessibility problem. Creative policy could expand availability considerably. For example, preparation and integration could be transformed into group therapy sessions, as piloted in a recent clinical trial of demoralization among people living with HIV. Similarly, psychedelics could be administered to cohorts of up to 6 people at once with shared guidance by trained monitors, as in a recent trial among healthy volunteers.”) (endnotes omitted).
184. FDA PSYCHEDELIC GUIDANCE, *supra* note 95, at 9; *id.* (“Examples of such professional credentials include the following: • Clinical or counseling psychologist (PhD or PsyD) • Psychiatrist or other physician (MD or DO) • Master of Social Work (MSW) • Licensed Clinical Professional Counselor (LCPC) • Licensed Marriage and Family Therapist (LMFT) • Psychiatric Nurse Practitioner (Psychiatric NP) Examples of such professional credentials include the following: • Clinical or counseling psychologist (PhD or PsyD) • Psychiatrist or other physician (MD or DO) • Master of Social Work (MSW) • Licensed Clinical Professional Counselor (LCPC) • Licensed Marriage and Family Therapist (LMFT) • Psychiatric Nurse Practitioner (Psychiatric NP)[.]”).
185. FDA PSYCHEDELIC GUIDANCE, *supra* note 95, at 9 (“Many of the psychedelic drug development programs involve administering the investigational drug and then engaging in psychological support or psychotherapy either while the subject is experiencing the acute effects of the drug or in a subsequent

- session. This additional variable both complicates the assessment of effectiveness and presents a challenge for any future product labeling. [¶] As of the publication date of this guidance, the contribution of the psychotherapy component to any efficacy observed with psychedelic treatment has not been characterized.”). There is considerable uncertainty in the law regarding the extent to which an agency’s guidance documents are entitled to deference when a statute is unclear or ambiguous. At one time, an agency’s interpretation was controlling unless its construction was unconstitutional or defied the text of the law. See *Bowles v. Seminole Rock & Sand Co.*, 325 U.S. 410 (1945); *Auer v. Robbins*, 519 U.S. 452 (1997). That is no longer true. In *Kisor v. Wilkie*, 139 S. Ct. 2400 (2019), four justices revised the *Seminole Rock–Auer* rule in favor of a multi-factor approach, while four other justices would have simply abandoned *Seminole Rock* and *Auer*. See Paul J. Larkin, Jr., *Agency Deference After Kisor v. Wilkie*, 18 GEO. J. L. & PUB. POL’Y 105 (2020). It is uncertain where the law will come to rest on this subject.
186. See Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845, 849 (2017) (noting the consensus that “state jurisdiction is reserved for medical *practice*—the activities of physicians and other health care professionals—while federal jurisdiction covers medical *products*, including drugs”) (emphasis in original; footnote omitted).
187. See *Dent v. West Virginia*, 129 U.S. 114 (1889) (ruling that a state may regulate the practice of medicine).
188. See *Gonzales v. Raich*, 545 U.S. 1 (2006) (ruling that Congress may outlaw the cultivation of cannabis as a drug even if it does not leave the state). Indeed, at one time the Supreme Court said that Congress could regulate the hands-on practice of medicine. See *Linder v. United States*, 268 U.S. 5, 18 (1925) (dictum that “direct control of medical practice in the States is beyond the power of the Federal Government”). The *Raich* case—and a host of other post-1925 Supreme Court decisions, see Paul J. Larkin, Jr., *Swift, Certain, and Fair Punishment: 24/7 Sobriety and HOPE: Creative Approaches to Alcohol- and Illicit Drug-Using Offenders*, 105 J. CRIM. L. & CRIMINOLOGY 39, 88–89 n.219–220 (2015) (collecting cases)—make the statement in *Linder* of dubious currency.
189. Paul J. Larkin, Jr. et al., *Telemedicine and Occupational Licensing*, 73 ADMIN. L. REV. 747, 750 (2021) (footnote omitted) (“Telemedicine is the real-time use of audio-visual technology to engage in remote transmission of necessary medical information to, and in communication with, a distant physician who can provide a diagnosis, recommend a course of treatment, and, if necessary, prescribe medication without first needing to be in the same physical location as a patient to conduct an in-person examination.”).
190. See *infra* note 284.
191. Congress could regulate interstate telephonic communications because they use an instrumentality of interstate commerce to practice medicine. See, e.g., *Fisher’s Blend Station v. Tax Comm’n of Washington*, 297 U.S. 650, 654 (1936) (“[S]ending telegraph or telephone messages across state lines... is interstate commerce”); *Western Union Tel. Co. v. Speight*, 254 U.S. 17, 18 (1920) (Holmes, J.) (“The transmission of a message through two states is interstate commerce as a matter of fact.”); *N.J. Bell Tel. Co. v. N.J. St. Bd. of Taxes & Assessments*, 280 U.S. 338 (1930 (by implication), *abrogated on other grounds by Okla. Tax Comm’n v. Jefferson Lines, Inc.*, 514 U.S. 175 (1995); cf. *Fisher’s Blend Station*, 297 U.S. at 654 (ruling that interstate radio broadcasting is interstate commerce). In criminal prosecutions, the federal circuit courts have uniformly recognized that Congress may regulate use of a nationwide communications system like a telephone or the Internet. See, e.g., *United States v. Covington*, 565 F.3d 1336, 1343 (7th Cir. 2009) (citing 18 U.S.C. § 1958(b) to establish that “[t]he telephone system is clearly a ‘facility of interstate...commerce’” and was actively used by the defendant to commit crimes); *United States v. Hornaday*, 392 F.3d 1306, 1311 (11th Cir. 2004) (“The internet is an instrumentality of interstate commerce.”); *United States v. Corum*, 362 F.3d 489, 493 (8th Cir. 2004) (“It is well-established that telephones, even when used intrastate, are instrumentalities of interstate commerce.”); *United States v. Gilbert*, 181 F.3d 152, 157–58 (1st Cir. 1999) (ruling that the telephone systems fit within interstate commerce); *Kerbs v. Fall River Indus., Inc.*, 502 F.2d 731, 738 (10th Cir. 1974) (“Both intrastate and interstate telephone communications are part of an aggregate telephonic system as a whole. And as long as the instrumentality itself is an integral part of an interstate system, Congress has power, when necessary for the protection of interstate commerce, to include intrastate activities within its regulatory control.”) (citation omitted). See *generally* Larkin et al., *supra* note 189, at 782 & n.117.
192. Larkin et al., *supra* note 189, at 779–85.
193. See *Scarborough v. United States*, 431 U.S. 563, 567–78 (1977) (ruling that the movement of a firearm in interstate commerce has an adequate nexus with commerce to permit a felon to be convicted of possessing a firearm under federal law).
194. See, e.g., ROBERT J. DURST, FUNNY, I DON’T REMEMBER ANY GOOD DOPE DAYS 26 (2023) (“Danielle got her supply of pills by going from pain clinic to pain clinic where she could gather up prescriptions for as many as 150 pills a month. Simple...easy peasy. [¶] Wait in line with about a dozen others and then out the door with a prescription and a \$75 charge, always payable in cash only, for a ‘pain analysis’ with a doctor whom she had never met or seen.”).
195. Whose effectiveness is in question. See A. Jay Holmgren & Nate C. Apathy, *Evaluation of Prescription Drug Monitoring Program Integration with Hospital Electronic Health Records by US County-Level Opioid Prescribing Rates*, 3 JAMA NETWORK OPEN e209085, at 1 (2020) (“Prescription drug monitoring programs (PDMPs) have become a widely embraced policy solution to the opioid epidemic in the US.... However, poor usability and lack of integration with electronic health records (EHRs) have limited their effectiveness.”) (footnotes omitted); Emily Rhodes et al., *The Effectiveness of Prescription Drug Monitoring Programs at Reducing Opioid-Related Harms and Consequences: A Systematic Review*, 19 BMC HEALTH SERVS. RSCH. 784, 793 (2019) (“Although we did not find evidence to strongly support the overall effectiveness of PDMPs in reducing opioid-related consequences and harms, if operationalized appropriately, they remain a valuable piece of a broader strategy to combat the opioid crisis. The mere presence of PDMPs is a reminder to physicians that they need to be careful when prescribing opioids.”).
196. See Briana Abbott & Daniela Hernandez, *Americans Take Ketamine at Home for Depression with Little Oversight*, WALL ST. J., Oct. 30, 2022, <https://www.wsj.com/articles/ketamine-depression-treatment-mental-health-home-11667059093> (“Startups are prescribing ketamine online to treat

serious mental-health conditions, raising concern among psychiatrists about the safety of taking the mind-altering anesthetic without medical supervision, sometimes at high doses that raise risks of side effects. [¶] Ketamine is approved by the Food and Drug Administration to anesthetize people and animals and has been used safely in hospitals for decades. The out-of-body, hallucinogenic sensations it produces made it popular as a party drug known as Special K. Some doctors prescribe ketamine off-label to treat patients with conditions including severe depression, suicidal thoughts and post-traumatic stress disorder.... Clinics that are certified to administer J&J's [Johnson & Johnson's] nasal spray must monitor patients for two hours afterward. [¶] People taking generic ketamine at home aren't subject to the same oversight. [¶] Mindbloom Inc., Nue Life Health PBC and Wondermed LLC are among around a dozen companies now selling ketamine tablets or lozenges online, making use of relaxed restrictions on the prescription of controlled substances during the pandemic. [¶] The companies work with clinicians who prescribe ketamine to patients based on a questionnaire and virtual evaluation. The generic ketamine pills or lozenges are mailed to patients' homes. The companies say they instruct people to take the medication with someone nearby, among other safety measures. [¶] Taking ketamine at home without medical supervision increases risks of patients falling and hurting themselves or taking more of the drug than prescribed, doctors said. Ketamine can be addictive, and patients might not get the help they need if they have a distressing experience while taking the drug, psychiatrists said. [¶] 'Places that are doing virtual ketamine are negotiating a compromise between accessibility and safety,' said Dr. Benjamin Yudkoff, medical director of the ketamine and esketamine program at Brigham and Women's Faulkner Hospital in Boston.".

197. Reardon, *supra* note 130, at 429 ("A MAPS spokesperson says that the organization expects that the drug's prescribing label will state that MDMA needs to be administered in combination with therapy. The FDA has done this previously with some other psychiatric drugs, including naltrexone. Because the FDA does not oversee behavioural-health interventions, the spokesperson adds, insurers or government payers are likely to enforce this requirement.").
198. "The greatest attention must be consistently given to establishing and maintaining strong safety parameters, and to that end ensure that investigator-therapists employ the highest ethical standards in their work. The nascent field must also guard against pathological narcissism and hubris." Grob & Grigsby, *supra* note 1, at xiii; *see also, e.g.*, Reardon, *supra* note 130, at 429 ("Safety problems, not necessarily with the drug itself, are also a concern. A woman enrolled in MAPS's phase II study reported that she had been assaulted by her therapists; videos show them lying in bed with her and kissing her during a 2015 MDMA session. One of the therapists later started a sexual relationship with her, and she eventually reported him to the police and sued him in civil court. In his response, the therapist said that the relationship was consensual. The case was settled out of court."); Smith, *Good Psychedelic Therapy*, *supra* note 108 ("While there is mounting evidence that psychedelics could offer much-needed new treatments for intractable mental illness, stories of abuse or trauma have also emerged—which have more to do with the therapists than the drugs. [¶] Some cases involve clear instances of sexual assault. With others, the therapist may have had good intentions but still caused more harm than healing. In one recent clinical trial, which found that psilocybin could offer relief for treatment-resistant depression, three participants reported having suicidal thoughts and harming themselves in the weeks following the therapy. [¶] Twenty years of research has standardized the dosage of the drugs used in clinical trials, but the therapy part has not received similar scrutiny. Instead, therapists' work is often based on tradition rather than empirical evidence, said Dr. Charles Raison, the director of clinical and translational research at the Usona Institute in Wisconsin and a professor of psychiatry at the University of Wisconsin.").
199. MAPS has proposed an ethical code that has been described as a good start but in need of supplementation. *See* Smith & Applebaum, *supra* note 90, at 3.
200. U.S. FOOD & DRUG ADMIN., *Risk Evaluation and Mitigation Strategies* (May 16, 2023), <https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rem> [hereafter FDA REMS]; *see* 21 U.S.C. § 355 (2018) ("(p) Risk evaluation and mitigation strategy [¶] (1) In general [¶] —A person may not introduce or deliver for introduction into interstate commerce a new drug if— [¶] (A)(i) the application for such drug is approved under subsection (b) or (j) and is subject to section 503(b); or [¶] (ii) the application for such drug is approved under section 351 of the Public Health Service Act; and [¶] (B) a risk evaluation and mitigation strategy is required under section 505-1 with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under section 505-1, including requirements regarding assessments of approved strategies."), § 355-1(a) ("(a) Submission of proposed strategy [¶] (1) Initial approval [¶] If the Secretary, in consultation with the office responsible for reviewing the drug and the office responsible for post[-]approval safety with respect to the drug, determines that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug, and informs the person who submits such application of such determination, then such person shall submit to the Secretary as part of such application a proposed risk evaluation and mitigation strategy. In making such a determination, the Secretary shall consider the following factors: [¶] (A) The estimated size of the population likely to use the drug involved. [¶] (B) The seriousness of the disease or condition that is to be treated with the drug. [¶] (C) The expected benefit of the drug with respect to such disease or condition. [¶] (D) The expected or actual duration of treatment with the drug. [¶] (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug. [¶] (F) Whether the drug is a new molecular entity. [¶] (2) Post approval requirement (A) If the Secretary has approved a covered application (including an application approved before the effective date of this section) and did not when approving the application require a risk evaluation and mitigation strategy under paragraph (1), the Secretary, in consultation with the offices described in paragraph (1), may subsequently require such a strategy for the drug involved (including when acting on a supplemental application seeking approval of a new indication for use of the drug) if the Secretary becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug.") (emphasis omitted).
201. FDA REMS, *supra* note 178.
202. *Id.*
203. *Id.* For a list of drugs with REMS, *see* U.S. FOOD & DRUG ADMIN., *Approved Risk Evaluation and Mitigation Strategies (REMS)* (Dec. 5, 2023).

204. Madras, *supra* note 73, at 1708–09: “Furthermore, can protocols for administering hallucinogens be scaled and retain fidelity to the plans used in trials?... The FDA is likely to require a Risk Evaluation and Mitigation Strategy to include rigid inclusion and exclusion criteria, limitations on dose and the number of doses, specialized therapy rooms and sessions, trained therapists, intensive sessions, a stringent chain of custody of the drug, and post[-]marketing surveillance and reporting. Costs associated with these conditions are likely to compromise adherence to the protocol and lead to a proliferation of unregulated clinics, as has happened with ketamine clinics.”).
205. See U.S. Att’y’s Off. E.D. Mo., *St. Louis Area Doctors Accused of Illegally Administering Ketamine, Health Care Fraud*, Jan.11, 2024, <https://www.justice.gov/usao-edmo/pr/st-louis-area-doctors-accused-illegally-administering-ketamine> (“Dr. Asim Muhammad Ali, 53, and Dr. Mohd Azfar Malik, 70, were each indicted on 22 felony counts: conspiracy to illegally distribute controlled substances and to maintain a drug-involved premises, conspiracy to commit health care fraud, 12 counts of illegal distribution of a controlled substance, seven counts of making false statements related to health care matters and one count of maintaining a drug-involved premises. [¶] The indictment says Dr. Ali, an internal medical specialist, defrauded Medicare when he falsely used Dr. Malik’s name and Medicare billing number to bill for health care services, including annual wellness visits. The indictment also says Dr. Ali illegally administered intravenous ketamine and a nasal spray version of the drug without authorization. [¶] Among businesses owned by Dr. Malik, a psychiatrist, was COPE Ketamine Clinic in south St. Louis County, the indictment says. COPE was created to provide intravenous ketamine infusions for serious mental health illnesses, such as treatment-resistant depression, anxiety disorders and post-traumatic stress disorder. [¶] Dr. Malik had a Drug Enforcement Administration registration authorizing him to administer controlled substances but not at the office suite housing COPE, the indictment says. He was also enrolled in the Spravato Risk Evaluation and Mitigation Strategy Program (REMS), which authorized him to administer the prescription esketamine nasal spray Spravato. Spravato is used to treat treatment-resistant depression and depressive symptoms in adults with major depressive disorder with suicidal thoughts or actions. Due to the risks of the drug, Spravato is only available through REMS and must be administered under the direct supervision of a healthcare provider who is onsite for at least two hours to monitor patients. [¶] Dr. Ali did not have a DEA registration and thus was not authorized to administer ketamine unless he was being directly supervised by and in the physical presence of a practitioner with a DEA registration, and only if the ketamine was being administered in a DEA-registered location, the indictment says. [¶] Dr. Ali was also suspended from participation in the Missouri Medicaid program in December 2020 and had a duty to report that to Medicare, it says. The indictment says he failed to do so and failed to fulfill his obligation to inform Medicare that he was providing services to Medicare beneficiaries through Dr. Malik’s businesses. [¶] The indictment alleges that beginning in December 2020, Dr. Malik and Dr. Ali agreed that Dr. Ali would use Dr. Malik’s DEA registration to administer ketamine infusions to patients without direct supervision by Dr. Malik and outside of Dr. Malik’s physical presence. Dr. Malik knew that Dr. Ali could not lawfully dispense controlled substances, including ketamine, without Dr. Malik’s physical presence and supervision, it says. Dr. Ali and Dr. Malik also determined that Dr. Malik could simply ‘say hi’ to the ketamine patients, typically via telephone, as a purported justification for Dr. Ali handling their ketamine treatment, the indictment says.”).
206. See *supra* note 63 & accompanying text.
207. “The [FDCA] prohibited the distribution in interstate commerce of adulterated’ foods and drugs. The act also empowered and directed the Commissioner of Food and Drugs to examine both products to be sure that they were safe for interstate distribution. In 1962, Congress also prohibited the distribution of new drugs unless and until the Commissioner has found that they are not only ‘safe,’ but also ‘effective.’ Ever since, Americans have entrusted the decision whether a particular new drug can be sold throughout the nation to experts at the Food and Drug Administration (FDA). Congress has reaffirmed that judgment on numerous occasions: in 1997, when it passed the Food and Drug Modernization Act of 1997; in 2007, when it enacted the Food and Drug Administration Amendments Act of 2007; in 2012, when it passed the Food and Drug Administration Safety and Innovation Act; and in other years as well. In fact, Congress implicitly but clearly reiterated its judgment every time that it passed an appropriations law underwriting the work of the Commissioner of Food and Drugs and his colleagues at the FDA.” Paul J. Larkin, Jr., *States’ Rights and Federal Wrongs: The Misguided Attempt to Label Marijuana Legalization Efforts as a “States’ Rights” Issue*, 16 *Geo. J. L. & Pub. Pol’y* 495, 500 (2018) (footnotes omitted).
208. *Supra* notes 33 & 97 and accompanying text.
209. *Supra* notes 102–03 and accompanying text.
210. See Larkin, *supra* note 106, at 527–30.
211. See Larkin, *supra* note 81, at 24.
212. “Though some herbal remedies do appear to be safe and effective, the opposite is closer to the truth. Cannabis is a good example. The number of parameters on which cannabis can vary is enormous from strain, growing conditions, harvesting methods and handling to storage and processing of the raw material to combining them with a wide variety of foods and other excipients in manufacturing to methods of administration (eating, smoking, ‘vaping,’ applying to mucous membranes). At every step, from planting through consumption, myriad influences can alter dose, absorption rate, interactions among constituents, exposure to toxins, and a host of other factors that can result in underdosing, overdosing and various types and levels of acute and chronic poisoning, not excepting an increase in the probability of lung cancer.” BRIAN F. THOMAS & MAHMOUD A. EL-SOHLI, *THE ANALYTICAL CHEMISTRY OF CANNABIS* xiii (2016); *id.* at 84; Larkin, *supra* note 81, at 9–23.
213. Smith et al., *supra* note 138, at 17 (“We support the decriminalization of psychedelic use and the protection of Indigenous practices, but we believe that policies such as Oregon’s outpace evidence on psilocybin’s safety. Experts generally agree that psychedelics can be used safely under medical supervision. However, most trials have excluded people at risk for bipolar disorder, psychosis, suicidality and many physical conditions (including diabetes, arrhythmias, seizure disorders and cardiovascular conditions). Questions remain about how safety data from these trials may generalize

outside carefully controlled research contexts; no data exist yet to support regulatory frameworks to ensure safety for psychedelic use. [¶] In our view, Oregon's regulations fall short in three areas, exposing service users to potential risks. [¶] First, consensus is emerging that informed consent standards for psychedelics should be more comprehensive than those for most psychoactive medications because the effects of these agents are atypical and often profound, and may be difficult to anticipate without prior experience.... Second, risk screening is a critical safety measure. At the moment, Oregon only requires service users to answer a few questions about potential risk factors, including those about lithium use, history of diagnosis or treatment for psychosis, and current or past ideation about suicide or harm to others.... Third, precautions should be enacted for safety monitoring during and after sessions, but Oregon requires no post-session monitoring, although it allows facilitators to conduct post-session integration.... Given the limited evidence on non-medical use, the safety concerns discussed above and 'psychedelic hype' that may mislead the public about risks and benefits, regulation may actually be more important for supported use than for clinical use.") (endnotes omitted).

214. See 21 U.S.C. § 841(a)(1) (2018); *supra* note 61.
215. See *United States v. Oakland Cannabis Buyers' Coop.*, 523 U.S. 483 (2001) (refusing to create an exception to the federal ban on cannabis distribution for cannabis distributed under the California medical cannabis regulatory program); Marks, *supra* note 106, at E2 (noting that the Colorado Natural Medicine Advisory Board, which assists in the drafting of implementing regulations for the state's new psychedelics law, "interprets Colorado's law to require state health insurance, funded by federal Medicaid, to cover health services offered in conjunction with unapproved psychedelic medicines. But Medicaid prohibits using its funds to support the use of Schedule I drugs such as marijuana and psychedelics, and requiring state insurance to cover related services could violate that prohibition and impermissibly involve the state in breaking federal law."). In addition, no Medicaid funds can be used to reimburse physicians, clinics, or hospitals for the use of Schedule I drugs. Marks, *supra* note 106, at E2. Trying to disguise their use by billing only for the psychotherapy that accompanies psychedelic treatment likely would amount to fraud or a violation of the Federal False Statements Act. *Id.*; see 18 U.S.C. §§ 1341 & 1342 (2018) (mail and wire fraud, respectively); 18 U.S.C. § 1001 (2018) (false statements).
216. Larkin, *supra* note 106, at 531; *id.* at 530–32 & nn.29–31. Those riders do not prohibit any particular effort to enforce the Controlled Substances Act of 1970 (or all of them combined) as long as the states are not "prevent[ed]" from allowing cannabis to be used under state law, but the U.S. Department of Justice, whether for legal or practical reasons (or both), has taken a mellow, laid-back, chilled-out approach to cannabis enforcement, so the federal cannabis laws are largely "on standby." *Id.* at 532 (footnote omitted).
217. See *supra* notes 97 and 102–03 and accompanying text.
218. Hamby, *supra* note 126 ("Because the Food and Drug Administration approved ketamine as an anesthetic more than 50 years ago, federal rules allow doctors to prescribe it for other conditions as well, and its use for depression, anxiety and post-traumatic stress disorder was growing before the pandemic.").
219. See U.S. FOOD & DRUG ADMIN., *FDA Alerts Health Care Professionals of Potential Risks Associated with Compounded Ketamine Nasal Spray*, Feb. 16, 2022 [hereafter FDA KETAMINE ALERT], <https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray> ("FDA is aware that some pharmacies compound nasal spray formulations of ketamine either alone or in combination with other ingredients, and there have been a concerning number of case reports of adverse events in recent years. Given these reports and the lack of standardized safety measures associated with the use of compounded ketamine nasal sprays, patients may be at risk of serious adverse events and potential misuse and abuse. FDA is issuing this alert due to the increased awareness of adverse events reported, the seriousness of these adverse events, and the likelihood that adverse events related to compounded drug products are under-reported, given that pharmacies that compound drugs under section 503A generally do not report them."); U.S. FOOD & DRUG ADMIN., *FDA Warns Patients and Health Care Providers About Potential Risks Associated with Compounded Ketamine Products, Including Oral Formulations, for the Treatment of Psychiatric Disorders* (Oct. 10, 2023) [hereafter FDA Ketamine Warning], <https://www.nytimes.com/2023/10/11/health/fda-ketamine-warning.html> ("Compounded drugs, including compounded ketamine products, are *not* FDA approved, which means FDA has not evaluated their safety, effectiveness, or quality prior to marketing. Therefore, compounded drugs do not have any FDA-approved indications or routes of administration. Although compounded drugs can serve an important medical need for certain patients when an FDA-approved drug is not medically appropriate, they also present a risk to patients and should only be used under the care of a health care provider. [¶] Use of compounded ketamine products *without* monitoring by a health care provider for sedation (sleepiness), dissociation (disconnection between a person's thoughts, feelings, and sense of space, time, and self), and changes in vital signs (such as blood pressure and heart rate) may put patients at risk for serious adverse events. [¶] Known safety concerns associated with the use of ketamine products include abuse and misuse, psychiatric events, increases in blood pressure, respiratory depression (slowed breathing), and lower urinary tract and bladder symptoms. For FDA-approved ketamine...the expected benefit outweighs these risks when used at appropriate doses for FDA-approved indications and routes of administration. [¶] Despite increased interest in the use of compounded ketamine, we are not aware of evidence to suggest that it is safer, is more effective, or works faster than medications that are FDA approved for the treatment of certain psychiatric disorders.") (emphasis in original); *supra* note 56 and accompanying text; see also Andrew Jacobs, *F.D.A. Issues Warning Over Misuse of Ketamine*, N.Y. TIMES, Oct. 11, 2023, <https://www.nytimes.com/2023/10/11/health/fda-ketamine-warning.html>.
220. See FDA Ketamine Warning, *supra* note 219: "The Spravato labeling contains a Boxed Warning that cautions that patients are at risk for sedation and difficulty with attention, judgment and thinking (dissociation), abuse and misuse, and suicidal thoughts and behaviors after administration of the drug. Because of the risk of sedation and dissociation, patients must be monitored by a health care provider for at least two hours after receiving their Spravato dose. The REMS requires the prescriber and the patient to both sign a Patient Enrollment Form that clearly states that the patient understands they should make arrangements to safely leave the health care setting to get home and that the patient should not drive or use heavy machinery for the rest of the day on which they received the drug. Additionally, Spravato must be dispensed with a Patient Medication Guide that outlines the drug's uses and risks. [¶] The patient self-administers Spravato nasal spray under the supervision of a health care provider in a

certified doctor's office or clinic, and the spray cannot be taken home. The health care provider will instruct the patient on how to operate the nasal spray device. During and after each use of the nasal spray device, the health care provider will check the patient and determine when the patient is ready to leave."

221. As Stanford Medical School Professor Dr. Smita Das has explained: "With respect to ketamine, clinics are advertising the treatment of many mental health disorders—and it's becoming increasingly popular. However, the protocols and approaches used by many clinics are not in national practice guidelines, or in some cases not well researched. Ketamine is only FDA approved as esketamine spray (Spravato) for medical use under supervision of a trained prescriber, and only for treatment resistant, severe unipolar major depression without psychotic features. Often, what is being administered in private clinics is not isolated ketamine and is not the nasal spray. In some cases, a psychiatrist or a physician isn't supervising, and it is not always being given for true treatment-resistant depression. Rather, the medication is being administered off-label. While this is common practice in medicine, it's generally after more research is available—which we don't have yet on ketamine. A 2017 consensus statement from the American Psychiatric Association provides an excellent summary and guidance on off-label use of ketamine given the state of the research to that point. At that time, only 147 cases were available." Smita Das, *KETAMINE CLINICS ARE JUMPING AHEAD OF THE EVIDENCE*, MEDPAGE TODAY, Feb. 5, 2023, <https://www.medpagetoday.com/opinion/second-opinions/102956>; see also Sophie Putka, *Ketamine via Telehealth: Psychiatrists Urge Caution*, MEDPAGE TODAY, July 28, 2022, <https://www.medpagetoday.com/special-reports/exclusives/99944> ("With a few online evaluations and a payment of \$359, you could have sublingual ketamine delivered to your doorstep. It's dispensed via Precision Compounding Pharmacy and can come as 'troches' that look like lozenges, or rapidly dissolving tablets. [¶] Psychiatrists and other professionals in the ketamine therapy space have questions about the rapid rise of telehealth to prescribe a drug traditionally reserved—and off-label—for the most stubborn cases of treatment-resistant depression. They raise concerns about the safety protocol of online-only services like Peak.... Experts say ketamine has some advantages over other depression treatments. It works quickly, providing fast relief, with effects felt in as little as 15 minutes. SSRIs, on the other hand, can take weeks to work. Quick relief from suicidal thoughts could mean the difference, for some patients, between life and death. Clinicians and patients report having transformational, even spiritual experiences with ketamine. [¶] But ketamine therapy is in its infancy, as is the scientific evidence to support its use in various contexts. [¶] Most published data pertain to intravenous ketamine or esketamine (Spravato), the only version of ketamine (an enantiomer [viz., a mirror-image molecule]) FDA-approved to treat depression. [¶] Data on sublingual ketamine are scarce—and evidence around its self-administered use at home is non-existent.... 'I think that's important that people aren't just taking it without anyone there,' said [Dr. Gail] Serruya. [¶] Then there are the actual physical effects. According to [Dr. Ryan] Henner, there's a 'significant loss of motor coordination at moderate to high doses.' So if a patient took ketamine at home, and 'God forbid something were to happen, they were to fall, they were to hurt themselves, it will be difficult for them to call for help, for instance.'... Ketamine 'does have a propensity to loosen and even dissolve the ego,' Ryan Henner, MD, staff psychiatrist and leader of the esketamine clinic at Beth Israel Deaconess Medical Center, told *MedPage Today*. So, he said, 'In person as opposed to over telehealth, if someone were having a distressing experience involving a loss of their sense of self, it certainly would be nice to have a supportive, understanding clinician available.' [¶] 'There's a lot also about ketamine, and in the ketamine experience, that we don't understand specifically around how it intersects with psychotic experiences,' said Henner, although he said providers do their best to screen out people at risk for psychosis.") (bracketed material added).
222. As the FDA has made clear, FDA Ketamine Warning, *supra* note 219 (emphasis in original): "Compounded drugs, including compounded ketamine products, are *not* FDA approved, which means FDA has not evaluated their safety, effectiveness, or quality prior to marketing. Therefore, compounded drugs do not have any FDA-approved indications or routes of administration. Although compounded drugs can serve an important medical need for certain patients when an FDA-approved drug is not medically appropriate, they also present a risk to patients and should only be used under the care of a health care provider. [¶] Use of compounded ketamine products *without* monitoring by a health care provider for sedation (sleepiness), dissociation (disconnection between a person's thoughts, feelings, and sense of space, time, and self), and changes in vital signs (such as blood pressure and heart rate) may put patients at risk for serious adverse events. [¶] Known safety concerns associated with the use of ketamine products include abuse and misuse, psychiatric events, increases in blood pressure, respiratory depression (slowed breathing), and lower urinary tract and bladder symptoms." As Dr. Das has explained: "Ketamine is also not without risks. Even esketamine spray, which has been studied and FDA approved, has boxed warnings with risks that include sedation, dissociation, and abuse or misuse, and is subject to strict controls on dispensing and administration under a risk evaluation and mitigation strategy (REMS) program. Physicians need to be trained in REMS, can only dispense esketamine spray in a healthcare setting, and are required to monitor patients for 2 hours after dispensation. [¶] If individuals attempt to use these substances on their own or in less structured clinics they risk acute adverse effects, for example a 'bad trip,' reckless behavior, worsening of psychiatric symptoms, panic, confusion, rapid heart rate, and possible interactions with other medications. There are also longer-term adverse effects of regular hallucinogen use such as persistent psychosis, Ketamine associated cystitis or bladder issues, or even developing a hallucinogen use disorder (addiction). Especially with off label use, the FDA has issued an alert about risks of compounded ketamine nasal sprays made by pharmacies (this is not the FDA approved esketamine, but ketamine). The alert cites cases of people experiencing side effects such as delusion, dissociation, visual hallucination, and panic attacks, as well as abuse and misuse. [¶] Some clinics may not screen patients for risk of adverse effects or whether they meet criteria for use (especially since there is little criteria for use). Furthermore, they may be offering these drugs for diagnoses other than depression, and they may not have psychiatric professionals available on staff. Some are using ketamine off label for other indications, such as pain, obsessive compulsive disorder, anxiety, and even substance use disorders. These clinics are often appealing, offering a fast treatment for long-time suffering. People with depression or other diagnoses may sink a lot of money into the treatments (as often these clinics do not take insurance) with false hopes of finding relief." Das, *supra* note 221.
223. Hamby, *supra* note 126.
224. The prior alert was issued in 2022. See FDA KETAMINE ALERT, *supra* note 219: "FDA is aware that some pharmacies compound nasal spray formulations of ketamine either alone or in combination with other ingredients, and there have been a concerning number of case reports of adverse events in recent years. Given these reports and the lack of standardized safety measures associated with the use of compounded ketamine nasal sprays, patients

may be at risk of serious adverse events and potential misuse and abuse. FDA is issuing this alert due to the increased awareness of adverse events reported, the seriousness of these adverse events, and the likelihood that adverse events related to compounded drug products are under-reported, given that pharmacies that compound drugs under section 503A generally do not report them.”

225. See *supra* note 227.
226. Tracy Wright & Adam Sabes, *Matthew Perry's Cause of Death Listed as "Acute Effects of Ketamine,"* Fox News, Dec. 15, 2023, <https://www.foxnews.com/entertainment/matthew-perry-cause-death-listed-acute-effects-ketamine>.
227. Raffi Djabourian, Senior Dpty. Medical Examiner, DEP'T OF MEDICAL EXAMINER, CNTY. OF LOS ANGELES, *Autopsy Report 1* (Dec. 14, 2023) [hereafter Perry Autopsy Report], https://www.theepochtimes.com/assets/uploads/2023/12/28/id5554761-2023-14789_Redacted.pdf; *id.* at 8 (“Mr. Matthew Perry’s cause of death is determined to be from the acute effects of ketamine. Contributory factors in his death include drowning, coronary artery disease and buprenorphine. The manner of death is accident (drug and drowning related). No signs of foul play are suspected in this death. At the high levels of ketamine found in his postmortem blood specimens, the main lethal effects would be from both cardiovascular overstimulation and respiratory depression. Drowning contributes to the likelihood of submersion in the pool as he lapsed into unconsciousness; coronary artery disease contributes due to exacerbation of ketamine induced myocardial effects on the heart. Buprenorphine effects are listed as contributory, even though not at toxic levels, due to the additive respiratory effects when present with high levels of ketamine.”); Fiore, *supra* note 180 (“Ketamine is not FDA-approved for treating any psychiatric disorder, but a derivative called esketamine (Spravato) is approved in nasal spray form for treatment-resistant depression. That product carries a boxed warning on sedation, dissociation, respiratory depression, abuse and misuse, and suicidal thoughts and behaviors. Nonetheless, ketamine is being investigated for and has shown some promise in numerous mental health conditions, including depression, anxiety, and post-traumatic stress disorder (PTSD).”).
228. Wright & Sabes, *supra* note 226; see Fiore, *supra* note 180 (“‘In clinical settings, ketamine is known for its safety profile. That doesn’t mean it is safe,’ psychiatrist Drew Ramsey, MD, of Spruce Mental Health in Jackson, Wyoming, wrote in an Instagram post. Ramsey noted a mixture of ‘celebrity, substance use disorders, character pathology, psychedelic medicine, and concierge medicine’ may have contributed to Perry’s death.... Andrew Stolbach, MD, MPH, a medical toxicologist with Johns Hopkins Medicine in Baltimore, who reviewed the autopsy report at the request of the Associated Press, said the amount of ketamine found in Perry’s blood ‘would be enough to make him lose consciousness and lose his posture and his ability to keep himself above the water.’ ‘Using sedative drugs in a pool or hot tub, especially when you’re alone, is extremely risky and, sadly, here it’s fatal,’ Stolbach told the AP.”).
229. Perry Autopsy Report, *supra* note 227, at 9.
230. *Id.*
231. *Id.* at 8 (“‘Toxicology testing reveals ketamine levels at 3540 ng/ml...in a peripheral blood source, and 3271 ng/ml in a central blood source.... For context, in monitored surgical anesthesiologic-care, levels for general anesthesia are typically in the 1000–6000 ng/ml ranges.”); see Fiore, *supra* note 180; Matt Stevens & Derrick Bryson Taylor, *Matthew Perry Died of "Acute Effects of Ketamine," Autopsy Says,* N.Y. TIMES, Dec. 15, 2023, <https://www.nytimes.com/2023/12/15/arts/matthew-perry-cause-death-friends.html?searchResultPosition=1> (“‘At the high levels of ketamine found in his postmortem blood specimens, the main lethal effects would be from both cardiovascular overstimulation and respiratory depression,’ the autopsy report said. It noted that the level of ketamine investigators found in Perry’s blood was equivalent to the amount that would be used during general anesthesia.”); Wright & Sabes, *supra* note 226.
232. See, e.g., GRINSPOON & BAKALAR, *supra* note 1, at 77 (noting that “the effects of LSD can sometimes be chaotic, painful, or terrifying.”); POLLAN, *supra* note 72, at 405 (“It is true I had a very positive experience using psilocybin ‘recreationally’—on my own, that is, without the support of a guide—and for some people this might be fine. But sooner or later, it seems, everyone has a trip for which ‘bad’ is far too pallid a modifier. I would hate to be alone when that happens.”); Yaden et al., *supra* note 162, at 943 (“It is also worth remembering that psychedelic treatments present real risks similar to virtually any effective treatment. These risks increase in recreational settings and include confusional states, abuse potential, and precipitation of enduring psychiatric conditions, particularly in persons with preexisting vulnerabilities ([e.g.,] psychotic disorders. Unfortunately, it is a matter of when, not if, a patient or participant will be harmed, and we need to do everything possible to prevent such tragedies”); *supra* note 146.
233. See Grinspoon, *supra* note 172 (“Psilocybin is generally thought to be safe in low dosages and has been used for centuries by indigenous peoples. However, if one takes too large a dose it can result in a terrifying—even traumatic—experience.”).
234. See, e.g., Jiang et al., *supra* note 77, at 8 (noting that the effect of ketamine might diminish “under continuous or repetitive administration,” a phenomenon known as tachyphylaxis, which could signal concern: “Given that Tachyphylaxis could affect the long-term efficacy of the drug, it’s crucial to closely monitor its therapeutic effect when using Esketamine for extended treatments and adjust treatment plans accordingly. Moreover, this study found that Euphoric mood, feeling of relaxation, and feeling drunk are adverse reactions associated with Esketamine use. They suggest an impact on emotional and mental states, potentially increasing the risk of drug abuse and addiction. The high incidence of suicidal ideation and suicide attempt underscores the importance of monitoring the mental state and suicidal risks of patients while administering Esketamine. [¶] Euphoric mood, feeling of relaxation, and feeling drunk, as potentially valuable adverse reactions during Esketamine use, indicate that the drug might carry a certain addiction potential.”); *id.* at 8 (“Overall, Esketamine not only demonstrates a significant antidepressant effect but also presents a range of AEs and potential risks. Particularly, concerning are the emergence of Tachyphylaxis, addiction risks, and suicidal risks during the treatment process, which require clinicians to pay close attention and implement appropriate interventions.”).
235. See GRINSPOON & BAKALAR, *supra* note 1, at 171–72; Adam Sabes, *Massachusetts Student Jumped Out of Sixth-Story Window After Taking Illegal "Magic Mushrooms,"* Fox News, Dec. 19, 2023, <https://www.foxnews.com/us/massachusetts-student-jumped-out-sixth-story-window-after-taking-illegal>

- magic-mushrooms. Such incidents, fortunately, are rare. GRINSPOON & BAKALAR, *supra* note 1, at 174 (“More easily available and commonly used drugs like alcohol, amphetamines, barbiturates, and phencyclidine create more danger of murder, suicide, and accidents than LSD, because they are taken much more casually and because they are more likely to provoke physical activity while impairing judgment and coordination.”).
236. See *supra* note 27.
237. Perry Autopsy Report, *supra* note 227, at 9 (noting that ketamine is used for recreational purposes because of its “‘dissociative’ nature, indicating disconnection of mind from body,” and “short duration hallucinatory and psychedelic” effects); see also, e.g., Fiore, *supra* note 180 (“It’s possible he was getting IV ketamine treatments and also illicitly abusing ketamine,” [Dr.] Ramsey told *MedPage Today*. “Illicit ketamine is fairly easy to get these days. There’s been an underground market for illicit ketamine for years.” [¶] There’s also been a ‘proliferation of ketamine clinics and at-home ketamine delivery,’ Ramsey said. ‘You can get screened and be treated by mail-order ketamine now.’ [¶] [Dr.] Das noted that this is occurring ‘without a clear set of guidelines or protocols’ on how to use these potential treatments appropriately. [¶] This likely spelled disaster for Perry, said Ramsey: ‘We have a polysubstance situation where there are a lot of meds on board, [and] this is someone who is already medically compromised, with coronary artery disease and a long-term history of substance use.’”) (first two bracketed items added; last one in original); Freedman, *supra* note 142, at 2389 (noting that “ketamine is also widely used recreationally”) (footnote omitted).
238. See, e.g., Ruan v. United States, 597 U.S. 450 (2022) (prosecution for unlawful distribution of opioids); United States v. Moore, 423 U.S. 122 (1975) (same, methadone); United States v. Ruan, 966 F.3d 1101, 1120 (11th Cir. 2020) (“The Superseding Indictment alleged that Ruan and Couch’s medical clinic was essentially a ‘pill mill,’ which prescribed controlled substances for no legitimate medical purpose or outside the usual course of professional practice.”); *id.* at 1123 (“From January 2011 to May 2015, Ruan and Couch prescribed more than 475,000 doses of TIRFs to over 1,000 patients. From 2012 to 2014, they sharply increased both the number of patients receiving TIRF prescriptions and the dosages prescribed. This practice placed the appellants among the top TIRF prescribers nationwide: they often surpassed the next highest prescriber by more than double. Despite these high numbers of TIRF prescriptions, no more than 15% of PPSA patients had cancer.”), *vacated and remanded on other grounds*, Ruan v. United States, 597 U.S. 450 (2022); United States v. Gowder, 841 Fed. Appx. 770, 777 (6th Cir. 2020); United States v. Oti, 872 F.3d 678, 684–90 (5th Cir. 2017); United States v. Azmat, 805 F.3d 1018, 1025–32, 1034–37 (11th Cir. 2015); Freedman, *supra* note 142, at 2390 (“Prescription drug–monitoring programs include ketamine as a Schedule III narcotic medication, but there are no barriers to stop a patient who has received ketamine in a referral clinic for severe depression from going to another provider who uses less stringent criteria to provide treatment. We need to remember that only a minority of physicians were responsible for the oxycodone epidemic.”) (footnote omitted).
239. *ER* (Constant C Productions et al. 1994–2009).
240. See Keith Humphreys, *Destigmatizing Drug Use Has Been a Profound Mistake*, ATLANTIC, Dec. 12, 2023, <https://www.theatlantic.com/ideas/archive/2023/12/destigmatizing-drug-use-mistake-opioid-crisis/676292/>.
241. See, e.g., SAM QUINONES, *THE LEAST OF US: TRUE TALES OF AMERICA AND HOPE IN THE TIME OF FENTANYL AND METH* (2021); J. Cobb Scott et al., *Neurocognitive Effects of Amphetamine: A Critical Review and Meta-analysis*, 17 NEUROPSYCHOLOGY REV. 275 (2007). See generally Paul J. Larkin, *Twenty-First Century Illicit Drugs and Their Discontents: Methamphetamines—The Downs of Ups or Tweaking the Night Away*, HERITAGE FOUND., Legal Memorandum (2023).
242. “Initially, amphetamines were seen as a valuable, safe, and nonaddictive pharmaceutical, a ‘wonder drug’ used for numerous purposes. For example, amphetamines opened bronchial and nasal passages, so they were used initially to treat asthma and nasal congestion. They also raised a user’s blood pressure, which helped patients with weak hearts or irregular heartbeats. Because amphetamines dissipate fatigue, fend off sleepiness, enhance peripheral vision and auditory ability, and generate alertness, clarity, endurance, perseverance, physical activity, well-being, and euphoric confidence, the military found their use enormously helpful. As long ago as the Spanish Civil War and during World War II, participants—including Germany, Japan, England, Canada, and the United States—distributed amphetamines to soldiers to remain vigilant while on duty. Amphetamines also had a wide range of nonmilitary uses. Physicians prescribed them as a pick-me-up, for weight loss, for libido enhancement, and for a host of other purposes. Long-haul truck drivers, college students behind on term papers or studying for exams, and professional athletes have used them to stave off fatigue and enhance their performance.” Larkin, *supra* note 241, at 2–3 (footnotes omitted); see also, e.g., LESTER GRINSPOON & PETER HEDBLUM, *THE SPEED CULTURE: AMPHETAMINE USE AND ABUSE IN AMERICA* 188 (1975): “The ‘crashing’ amphetamine abuser lacks the energy to complain and may seem to be merely exhausted and in need of sleep. Recently investigators have looked more closely, and the emerging picture is unpleasant and painful. Extreme lethargy and fatigue are almost invariably reported. Although the ‘crasher’ may sleep for several days, he never sleeps well, and often wakes screaming from nightmares. On awakening, he may experience anxiety attacks and suicidally severe depression. His psychic disruption and loss of self-control may lead to violent acting out of sexual conflicts and aggressive impulses. He often experiences acute fear and terror and is as likely to turn homicidal as suicidal. He is apt to be extremely irritating and demanding, driving people away just when he most needs their help. His head aches; he may have trouble breathing; he sweats profusely; his body is racked by alternating sensations of extreme heat and cold and distressing muscle cramps. He may feel so exhausted that he is unable even to stand. He is characteristically constipated, and suffers painful gastrointestinal cramps.”
243. Larkin, *supra* note 241, at 4–5 (footnotes omitted): “As the ‘rush’ wears off, the user ‘crashes,’ with fatigue, restlessness, nervousness, agitation, anxiety, irritability, and depression replacing nirvana. The comedown from crystal meth is famously wicked: The user thinks that a repeat meth performance will end that distress and restore bliss. ‘The urge to repeat the drug experience is often irresistible.’ Because ‘[t]he intensity of that rush is dose-related,’ meth users tend to make their third mistake: They consume increasingly higher doses, increase the frequency of their meth use, or both. The result is ‘a cycle of additional doses and increasing overall cumulative dose’—a ‘run’ that can last for several days,’ an experience common to users known as ‘speed freaks.’ That spells trouble. The brain has now been taught to seek methamphetamine relentlessly in order to reproduce that experience. [¶] Repeated cycles of meth use—a user’s fourth, fifth, sixth, seventh, etc., mistakes—repeat the feeling of ‘crashing’ and render a user severely dependent

on the drug. He is now in a wrestling match with a drug that won't tap out; his life is now 'a complete preoccupation with the drug and its effects.' That is when the user's real nightmare begins, because meth has 'hijacked' the brain's higher reasoning functions. [¶] The vast majority of meth users do not become addicted to the drug—which is fortunate. Long-term users can suffer from a host of adverse physical and psychological outcomes either from meth use alone or from polydrug use, a common practice among speed freaks. The adverse physical effects include dehydration, hyperthermia, hypertension, malnutrition, cachexic-like weight loss, damage to the cardiovascular system and the brain's blood vessels, an expedited aging process, ulcerated regions of the skin due to scratching at 'meth bugs,' 'meth mouth,' and hepatitis or HIV/AIDS from sharing needles. It is as if 'a person is literally falling apart from the inside out.' [¶] Psychological problems include a diminished ability to concentrate, incoherent thought processes, mild-to-moderate neuropsychological impairment, anxiety and poor impulse control, depression, confusion, sleeplessness, paranoia, delusions, and visual or auditory hallucinations (e.g., 'seeing angels and demons' or believing that 'God spoke to [a user] through people on television'). Users can die from the sequelae of drug use (e.g., hypertension-caused hemorrhagic stroke). Addiction leaves chronic users with 'a brainwashed slavery that deprives [them] of free will and turns [them] towards self-harm in the search for dope.' [¶] Finally, chronic (or high dose) meth use can also damage the nervous system's ability to produce dopamine, a compound necessary for non-drug-induced feelings of pleasure. Depletion of the body's dopamine reserves and damage to its dopamine-production capacity can leave users suffering from anhedonia (in this case the inability to experience pleasure from anything other than meth use) as well as from Parkinson's Disease-like behavior and an unquenchable rage."

244. See, e.g., Brianna Abbott & Daniela Hernandez, *As Psychedelics Become More Mainstream, Here's What You Need to Know*, WALL ST. J., June 27, 2023, https://www.wsj.com/articles/psychedelics-ketamine-ld-drug-what-to-know-d552ee9c?mod=Searchresults_pos6&page=1; Alison Gopnik, *The New Promise of Psychedelics*, WALL ST. J., July 20, 2023, https://www.wsj.com/articles/the-new-promise-of-psychedelics-2280c3b?mod=Searchresults_pos7&page=1; Daniela Hernandez & Brianna Abbott, *Drug Companies Join Medical Psychedelic Movement—but Without the High*, WALL ST. J., Dec. 18, 2022, https://www.wsj.com/articles/drug-companies-join-medical-psychedelic-movement-but-without-the-high-11671319811?mod=Searchresults_pos1&page=1&mod=article_inline; Daniela Hernandez, *Psilocybin, Psychedelic Compound in Magic Mushrooms, Shown Effective for Alcohol Addiction*, WALL ST. J., Aug. 24, 2022, https://www.wsj.com/articles/psychedelic-compound-in-magic-mushrooms-shows-new-promise-as-alcohol-addiction-treatment-11661354909?mod=article_inline. *The Wall Street Journal* reported that "Elon Musk takes ketamine," Grind & Bindley, *supra* note 120; see Emily Glazer & Kirsten Grind, *Elon Musk Has Used Illegal Drugs, Worrying Leaders at Tesla and SpaceX*, WALL ST. J., Jan. 6, 2024, <https://www.wsj.com/business/elon-musk-illegal-drugs-e826a9e1>, but Musk denied illicitly using drugs or using illegal drugs, Alyssa Lukpat et al., *Elon Musk Criticizes WSJ Reporting on His Use of Illegal Drugs*, WALL ST. J., Jan. 8, 2024, https://www.wsj.com/tech/elon-musk-criticizes-wsj-reporting-on-his-use-of-illegal-drugs-c268d0fb?reflink=integratedwebview_share.
245. "In pharmacology, 'microdosing' generally describes the administration of a minute quantity of a drug—generally no more than one percent of the active compound, up to 100 µg—to determine its pharmacokinetics [viz., its effect on the body]." PASSIE, *supra* note 44, at 3. Psychedelic microdosing involves a greater percentage of the active compound, but a smaller quantity. *Id.* at 3–4, 1, 47–61; Kim P.C. Kuypers et al., *Microdosing Psychedelics: More Questions Than Answers? An Overview and Suggestions for Future Research*, 33 J. PSYCHOPHARMACOLOGY 1039, 1040 (2019) ("[P]sychedelic microdosing ('5–10 µg of LSD'...) would be 5–10% of a usual psychoactive dose and lie between a full pharmacological dose (100%) and a 'pharmacological microdose'.") (citation omitted); Nutt et al., *supra* note 52, at 26 ("Microdosing involves taking—usually on a regular basis, e.g., 3 times a week—a low dose of a psychedelic that is devoid of psychoactive effects."); Dana G. Smith, *More People Are Microdosing for Mental Health. But Does It Work?*, N.Y. TIMES, June 23, 2023 [hereafter Smith, *Microdosing*], <https://www.nytimes.com/2022/02/28/well/mind/microdosing-psychedelics.html?searchResultPosition=6> ("Microdosing is typically defined by experts as taking 5 percent to 10 percent of a full dose of a psychedelic, usually LSD or psilocybin, as a way to get the supposed mental health benefits of the drug without the hallucinogenic high. For instance, in a clinical setting, a 155-pound man might take 20 milligrams of psilocybin for a full psychedelic experience. For a microdose, he'd take only one to two milligrams. At that level, taken several times a week, some claim the drugs improve their mood, boost their creativity and give the world a brighter, shinier quality, like it's in high-definition.").
246. PASSIE, *supra* note 44, at 11, 61–74. Minidoses are in the 25–50 µg range. *Id.* at 11 (referring to LSD). "To some therapists and researchers these doses seemed useful because they 'activate' the psyche. Low doses enhance sensitivity, the perception of emotions, and might provoke memories and catharsis." *Id.* Some but not all psychological tests have found performance deficits with doses in this range. *Id.*
247. See *supra* note 67 and text accompanying note 69.
248. PASSIE, *supra* note 44, at i.
249. *Id.*
250. Grinspoon, *supra* note 172 ("Does microdosing work? In short, the jury is still out. Some studies indicate a very real and significant benefit from microdosing, whereas others are much less convincing and show little to no benefit. One recent study used a naturalistic, observational design to study 953 psilocybin microdosers compared with 180 nondosing participants for 30 days, and found 'small to medium-sized improvements in mood and mental health that were generally consistent across gender, age, and presence of mental health concerns.' This study and others like it appear to confirm many anecdotal reports of people who swear by the benefits they have experienced from microdosing. [¶] Other studies on microdosing are far less impressive.... [¶] It is important to understand that there isn't yet definitive proof that microdosing is at all helpful, or even that it is safe in the long term."); Smith, *Microdosing*, *supra* note 245 ("So many of the scientists who pioneered research into full doses of psychedelics have started studying whether a microdose might also be beneficial. But evidence is limited, and experts are divided about how microdosing helps people—or if it does at all. [¶] Much of the early research into microdosing has been anecdotal, consisting of enthusiastic survey responses from users who experienced enhanced attention and cognition, feelings of well-being and relief from anxiety and depression. Lab studies of psilocybin and LSD microdoses tend to support these claims, showing improvements in mood, attention, and creativity. But these studies have generally been small, and

- they didn't compare a microdose to a placebo. [¶] 'You probably only participate at this point in a trial in microdosing if you really have a strong belief that this might help you,' said Dr. David Erritzoe, clinical director of the Centre for Psychedelic Research at Imperial College London. And when people expect to benefit from a drug, they typically do.").
251. See, e.g., Abbott & Hernandez, *supra* note 244 ("Universities and clinics are studying whether the drugs can treat health conditions including post-traumatic stress disorder and depression. Investors have taken notice—pouring money into psychedelic-drug development, with the market expected to reach \$11.8 billion by 2029, according to the research firm BrandEssence."); Grind & Bindley, *supra* note 120 ("The value of the psychedelic drug market, which includes companies engaging in research and trials to legalize the use, is expected to reach \$11.8 billion by 2029, up from \$4.9 billion in 2022, according to research firm BrandEssence. Founders Fund has an ownership stake in Compass Pathways, a company researching commercial psilocybin development, and its co-founder Peter Thiel is personally invested in Atai Life Sciences, which is developing psychedelics for mental health."); *Psychedelic Hope and Dilemma*, *supra* note 91 ("It is estimated that the psychedelics market could be worth more than US\$8 billion by 2028[.1]"); *Investors*, *supra* note 75 ("Messrs. Angermayer and Thiel are not alone in putting money into the medical application of psychedelics. A clutch of investors see these drugs going the way of cannabis, whose creeping decriminalisation has spurred commercial interest in the weed's medical uses. In particular, backers think, psychedelic drugs could be used to treat mental-health disorders like depression, anxiety and addiction.").
252. See *Bosses Want to Feed Psychedelics to Their Staff. Are They High?*, *ECONOMIST*, June 8, 2022, <https://www.economist.com/business/2022/06/08/bosses-want-to-feed-psychedelics-to-their-staff>.
253. See Hall, *supra* note 49, at 28–29; Madras, *supra* note 73, at 1709. As Wayne Hall has explained: "There is a real possibility that psychedelic drugs may follow the example set by 'medical cannabis'. First, some advocates of psychedelic drugs are seeking approval to use these drugs before they have been approved for medical use by using the same compassionate access provisions that were used to allow medical cannabis use.... Allowing access via special access schemes before formal regulatory approval may allow the use of MDMA to treat all anxiety disorders, various types of addiction, and patients with terminal illnesses. We may also see lobbying for compassionate access to other psychedelic drugs such as LSD, mescaline, and DMT. [¶] Second, attempts are being made in the USA to use popular referenda to legalise the adult use of psychedelic mushrooms...the same approach used by advocates after California became the first US state to permit physicians to prescribe cannabis if they 'deemed [it] appropriate' in 1996.... Some states may legislate to give patients the right to try psychedelic drugs. The medical cannabis industry in the USA is also investing in companies that produce psychedelic drugs.... These policies would enable the medical use of psychedelics to get well ahead of any evidence on their efficacy and safety for common psychiatric indications, as has happened with medical cannabis.... [¶] We can also expect arguments to be made for allowing patients to use plant-based psychedelic drugs, such as mushrooms, ayahuasca and ibogaine, because of the putative 'entourage' effects of the whole plant.... These claims appeal to a popular cultural meme that 'natural' medicines derived from whole plants are safer and more effective than 'synthetic' pharmaceuticals, a meme often used by the 'medical cannabis' industry." (citations omitted). Hall, *supra* note 58, at 28–29.
254. Madras, *supra* note 73, at 1709; see also Lieberman, *supra* note 62, at 1461 ("We should not ignore the unusual process by which psychedelics are being developed. This process markedly deviates from conventional models of drug development in which candidate compounds are screened against validated biologic targets and the most promising is selected to test in humans. The unconventional nature of psychedelic drug development is highlighted by the outsized investments they have attracted despite the limited patent protection of existing compounds.").
255. Volkow et al., *supra* note 62, at 979.
256. *Id.*
257. Paul J. Larkin, Jr., *Medical or Recreational Marijuana and Drugged Driving*, 52 *AM. CRIM. L. REV.* 453, 468 (2015).
258. *Marijuana for the Sick*, *N.Y. TIMES* (Dec. 30, 1996), <http://www.nytimes.com/1996/12/30/opinion/marijuana-for-the-sick.html> ("Supporters of the California measure did their cause no good by immediately lighting up marijuana cigarettes after it passed last month and proclaiming that a legitimate medicinal use would include smoking a joint to relieve stress. Dennis Peron, originator of the California initiative, said afterward, 'I believe all marijuana use is medical—except for kids.' These actions made it obvious that the goal of at least some supporters is to get marijuana legalized outright, a proposition that opinion polls indicate most Americans reject.").
259. Larkin, *supra* note 257, at 511–12 ("California does not require patients to register to receive marijuana for medical use, so the number of patients is a matter of speculation. Estimates, however, are that the number increased from 30,000 in 2002 to more than 300,000 in 2009 and 400,000 in 2010. The California statute permits a patient or caregiver to possess six plants, but it allows counties to amend state guidelines. Humboldt County, which lies in the heart of the Northern California marijuana farming, allows resident[s] to grow up to ninety-nine plants on behalf of a patient. Not surprisingly, there is also considerable evidence that significant quantities of marijuana grown or sold for medical uses have been diverted for recreational use.") (footnotes omitted), 513 n.283 (collecting authorities).
260. *Id.* ("It turns out, however, that the number of registered medical marijuana 'patients' is far too large to believe that only the seriously afflicted are taking advantage of these new laws. The number of users gives strong reason to believe that a massive number of medical marijuana patients are not the poor suffering individuals on whom those laws were supposed to focus—people nearing the end of life or suffering from a debilitating disease or chronic pain. Instead, it is not unreasonable to believe that medical marijuana legislation is a sleight of hand to do indirectly what the new recreational marijuana laws do directly—allow individuals to use marijuana without risking state law criminal liability. It is fair to say that the only difference between medical marijuana laws and recreational marijuana laws [is] that the latter are honest in their goals. [¶] There is considerable proof that many state medical marijuana programs are simply a sham for the decriminalization of that substance. Consider the following: according to a 2013 study, in Arizona merely seven of 11,186 applications for medical marijuana had been denied. Only 2,000 patients registered for Colorado's medical marijuana program before the Justice Department announced in 2009 that it would not enforce the federal marijuana laws against individual patients

- and caregivers. Colorado residents apparently listened because by March 2011, there were more than 127,000 Colorado registrants. In Colorado, fewer than fifteen physicians wrote more than seventy percent of all medical marijuana recommendations, with the reason being severe or chronic pain in ninety-four percent of the reported conditions. Michigan had fifty-five physicians certify approximately 45,000 patients.”) (footnotes omitted).
261. NIDA Director Volkow told Congress in 2020 that “in general, adequate and well-controlled studies” have not established that the botanical cannabis sold in states with legalized medical-use or recreational-use régimes satisfied the Food, Drug, and Cosmetic Act requirement for new drug approval. Statement of Nora Volkow, Dir., Nat’l Inst. on Drug Abuse 7 (Jan. 15, 2020), in *Cannabis Policies for the New Decade: Hearing Before the House Commerce Comm. Subcomm. on Health*, 116th Cong. (2020). A result is that “individuals across the country are using cannabis strains and extracts that have not undergone the rigorous clinical trials required to show that they are safe and effective for medical use, and are not regulated for consistency or quality.” *Id.*
262. See Boehnke et al., *supra* note 178, at 1 (“The déjà vu with cannabis policy is remarkable. Over the past 25 years, cannabis liberalization advanced quickly, justified by arguments for compassionate use and personal freedom and frustration toward national drug policies. Indeed, despite federal criminalization, cannabis products are a mainstay in many states, supported by the considerable unmet need for alternative therapies aimed at difficult-to-treat conditions, such as chronic pain; changing public perceptions; and exponential market growth. Similarly criminalized and supported by comparable arguments, psychedelics are poised to follow a parallel pattern, reinforced by the US Food and Drug Administration designating psilocybin and 3,4-methylenedioxyamphetamine (MDMA) as breakthrough therapies for major depressive disorder and posttraumatic stress disorder, respectively. With this context, we believe that the momentum behind psychedelic decriminalization is unlikely to diminish. Thus, to effectively navigate forward with psychedelics, it would be wise to learn from the lessons of cannabis liberalization.... Scientific inquiry around therapeutic uses of cannabis was stifled by federal drug policy, so qualifying conditions were strongly influenced by patient advocacy, rather than comprehensive scientific data.”) (endnote omitted); Madras, *supra* note 73, at 1709.
263. Madras, *supra* note 73, at 1709.
264. *Id.*
265. Londono, *supra* note 106 (“Psychedelics, a class of psychoactive substances that alter mood and perception, have long been illegal. But stigma surrounding their use has receded in recent years as scores of celebrities, military veterans, athletes and entrepreneurs have described psychedelic trips as transformative experiences and opportunities for self-exploration and spiritual growth.”); Smith, *Good Psychedelic Therapy*, *supra* note 108 (“There has also been a shift in how the drugs are presented in popular culture and the media, like in Michael Pollan’s best-selling book and Netflix series, ‘How to Change Your Mind.’ Two states, Oregon and Colorado, have now legalized psilocybin for therapeutic use, and more are expected to follow suit. [¶] As these drugs gain mainstream acceptance, more and more people will likely consider taking them, both therapeutically and recreationally.”).
266. See Smith, *Dangerous Psychedelics*, *supra* note 138 (“Experts who study these substances strongly urge that people only use them in supervised therapeutic settings, such as in a clinical trial or at an established ketamine clinic, partly because of safety concerns and partly because they are illegal outside of these confines. Realistically, though, many people will use them elsewhere.”).
267. I have written about this subject often enough to feel like a latter-day Cicero reiterating “*Delenda est Carthago*” in the Roman Senate. See, e.g., Paul J. Larkin, *Driving While Stoned in Virginia*, 59 AM. CRIM. L. REV. ONLINE 1 (2022) [hereafter Larkin, *Driving While Stoned in Virginia*]; Larkin, *supra* note 106, at 554–60; Paul J. Larkin, Jr., *Reconsidering Federal Marijuana Regulation*, 18 OHIO ST. J. CRIM. L. 99, 135–41 (2020); Larkin, *supra* note 256.
268. Other researchers report that the effects can last for a longer period than “several hours.” See, e.g., GRINSPOON & BAKALAR, *supra* note 1, at 14–19 (noting that the psychoactive effect of LSD and ibogaine lasts for 8–12 hours; for psilocybin, 4–6 hours; for mescaline, 8–12 hours); NUTT, *supra* note 21, at 47 (MDMA, 6–8 hours; ibogaine, usually 24 hours, but could last for 72 hours); Grob et al., *supra* note 52, at 71 (noting that psilocybin’s effect can last for 4–6 hours).
269. “Mistaken perceptions of perspective were also reported. A tablespoon appeared to be as long as a ladle. The subjects’ own hands appeared sometimes large and plumb, and at other times distant and small.... Time was experienced sometimes as moving more slowly than normal, or sometimes as moving faster, or even as having stopped.” PASSIE, *supra* note 44, at 64, 66; Ross et al., *supra* note 29, at 186.
270. See PASSIE, *supra* note 44, at 64 (noting that minidosing subjects experienced visual hallucinations, but “the test subjects were always aware that the phenomena were not real”).
271. See, e.g., GRINSPOON & BAKALAR, *supra* note 1, at 172; PASSIE, *supra* note 44, at 6 (“[Psychedelics users] should be aware that microdosing and (especially) minidosing [viz., taking a small amount of the drug just above the level that generates noticeable psychoactive effects, *id.* at 11] can compromise their everyday performance,” including “handling complex machinery.”); *id.* at 138 (“[W]ith doses in the range of 25–50 µg some deficits in performance (e.g.,] driving, behavior in complex social or stressful situations) might be present, and put the user at risk.”). But see *id.* at 162–63 Tbl. 17 (noting that moderate [50 µg] doses of LSD resulted in “no significant change” in “Attention and concentration” and “Reaction time”).
272. LEARY ET AL., PSYCHEDELIC EXPERIENCE, *supra* note 2, at 5.
273. FDA Ketamine Approval, *supra* note 97.
274. Psychedelics are unlikely to pose a greater societal problem of driving impairment than liquor or cannabis, for two reasons: Far fewer people use psychedelics, and “the acute effects of classic psychedelics are so disrupting that persons under their influence are less likely to drive than those who are under the influence of intoxicating, sedating, and inhibition releasing substances that are more commonly associated with traffic accidents and fatalities.” Johnson, *supra* note 48, at 158. The first rationale is empirically based, and it comports with common experience. The second rationale,

however, is more an educated guess than an empirical judgment. What troubles me is the evidence that some number of people who are under the influence of cannabis believe that they are better drivers when high than straight. Larkin, *Driving While Stoned in Virginia*, *supra* note 267, at 7–8 (“Unfortunately, a goodly number of users reported driving under the influence of cannabis. What is worse, a considerable number of individuals believe that cannabis use does not impair their ability to drive safely (or actually improves their driving skills), a conclusion that is demonstrably false.”) (footnotes omitted); *id.* at 8–9 n.27 (collecting authorities). Some psychedelics users could hold the same belief.

275. U.S. NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION, DRUGS AND HUMAN PERFORMANCE FACT SHEETS 52 (2014).

276. *Id.*

277. *Id.*

278. Some have. See Mithoefer & Mithoefer, *in* Grob & Grigsby, *supra* note 1, at 257 (recommending a treatment protocol as part of an FDA Risk Evaluation and Mitigation Strategy that includes a requirement that “[d]riving [be] prohibited for five half-lives of MDMA”). More should do so too.

279. See, e.g., Emory N. Brown et al., *General Anesthesia, Sleep, and Coma*, *NEW ENG. J. MED.* 2638, 2647–48 (2010) (“The fact that general anesthesia can be functionally equivalent to brain-stem death indicates how deeply general anesthesia can depress brain function and perhaps explains why some patients do not fully recover consciousness for several hours after general anesthesia and why postoperative cognitive dysfunction could persist in elderly patients for several months.”); Frances Chung et al., *What Is the Driving Performance of Ambulatory Surgical Patients After General Anesthesia?*, 103 *ANESTHESIOLOGY* 951, 954 (2005) (“In this study, the patients showed attention lapses, lower alertness levels, and poor lane accuracy preoperatively. Sleepiness, fatigue, and alertness returned to normal levels by 24 h. There was no association between duration of an anesthetic and driving ability.”), 955 (“Many ambulatory surgery patients meet discharge criteria within 2–3 h after general anesthesia. We have demonstrated that patients are significantly sleepier and less alert 2 h after anesthesia. This was reflected in driving performance parameters, and subjective assessments of sleep and fatigue and visual analogue alertness scores. These findings at 2 h after anesthesia support current recommendations for patients to be discharged with a responsible adult as an escort.”).

280. See, e.g., PASSIE, *supra* note 44, at 168 (“Potentially, doses of LSD of 20 µg or above can lead to noticeable decreases in performance of daily routines, especially when it comes to more elaborate tasks such as car driving, handling machinery or complex (theoretical or practical) work issues. In conclusion, it is generally not recommended to take doses of more than 15 µg if one is supposed to perform as usual (or better). Special care must be taken if potentially life-threatening activities such as rock climbing or car driving are to be done.”); Belouin & Henningfield, *supra* note 52; Louisa Degenhardt et al., *Driving, Drug Use Behaviour and Risk Perceptions of Nightclub Attendees in Victoria, Australia*, 17 *INT’L J. DRUG POLICY* 41 (2006); R. Giorgetti et al., *Effects of Ketamine on Psychomotor, Sensory and Cognitive Functions Relevant for Driving Ability*, 252 *FORENSIC SCI. INT’L* 127 (2015); A.W. Jones et al., *Driving Under the Influence of Psychoactive Substances—A Historical Review*, 31 *FORENSIC SCI. REV.* 103 (2019); Johnson et al., *supra* note 48, at 154 (noting that a dose of psilocybin higher than microdosing can “result[] in strong and possibly overwhelming psychological effects in a dangerous or otherwise problematic environment, for example, while driving or working”); Christopher P. Salas-Wright et al., *Driving While Under the Influence of Hallucinogens—Prevalence, Correlates, and Risk Profiles*, 228 *DRUG & ALCOHOL DEPENDENCE* 109055, at 5 (2021) (noting that although only 2.5 percent of the population reports using hallucinogens, nearly 10 percent of those users report “driving under the influence of substances we know distort one’s perception of reality, including visual and auditory hallucinations and the feeling of disconnection from one’s body and surroundings,” which “translates to several hundred thousand individuals driving automobiles over the course of the year while experiencing hallucinations and dissociative states”); *id.* at 5–7 (finding that regular psychedelic users are more likely to drive under their influence than sporadic users and are also more likely to report driving under the influence of alcohol, cannabis, and other illicit drugs); *id.* at 7 (“[O]ur findings make clear that a disconcerting number of hallucinogen users report DUIH [driving under the influence of a hallucinogen]. Not only is this behavior illegal, but it also likely—based on prior research on the effects of hallucinogen use and their impact on skills needed for safe driving—places others at risk.”); *cf.* U.S. NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION, DRUGS AND HUMAN PERFORMANCE FACT SHEETS 65 (2014) (describing why methamphetamine users should not drive); PERRY N. HALKITIS, *METHAMPHETAMINE ADDICTION: BIOLOGICAL FOUNDATIONS, PSYCHOLOGICAL FACTORS, AND SOCIAL CONSEQUENCES* 57 (2009) (suggesting that “use of the drug is associated with persistent physiological changes to the brain that lead to slower reaction times in examinations of cognitive function”), 59 (noting that meth can impair recall and the ability to manipulate information, perform abstract reasoning, and ignore irrelevant data); HAL MARKOVITZ, *METHAMPHETAMINE* 54 (2006) (“People who ingest methamphetamine have no business getting behind the wheel of a car.”); K.P.C. Kuypers et al., *MDMA and Alcohol Effects, Combined and Alone, on Objective and Subjective Measures of Actual Driving Performance and Psychomotor Function*, 187 *PSYCHOPHARMACOLOGY* 467 (2006); Allison Jane Matthews et al., *Driving Under the Influence Among Frequent Ecstasy Consumers in Australia: Trends Over Time and the Role of Risk Perceptions*, 144 *DRUG & ALCOHOL DEPENDENCE* 218 (2014); *cf.* Karel A. Brookhuis et al., *Effects of MDMA (Ecstasy), and Multiple Drugs Use on (Simulated) Driving Performance and Public Safety*, 173 *PSYCHOPHARMACOLOGY* 440, 440, 442 (2004) (noting that MDMA alone increases drivers’ reaction time and the combination of MDMA with other drugs, such as alcohol or cannabis, is certainly dangerous).

281. Salas-Wright et al., *supra* note 280, at 1 (citation omitted).

282. *Id.* at 2 (citation omitted).

283. Larkin, *supra* note 132, at 482–83.

284. “Society has known the fatal consequences of drunk driving since automobiles were invented. Beginning in the 1980s, however, society resolutely chose to reduce what had previously become an increasing slaughter on our highways that had reached the astounding figures only heard of on the battlefield. The federal and state governments aggressively implemented multi-step programs to reduce that bloodshed. Among them were the following: legislation fixing the maximum blood-alcohol content (BAC) at 0.08 grams per deciliter (g/dL), mandatory license suspension penalties for

- conviction, more aggressive prosecution of drunk drivers, and public education and advocacy by organizations such as Mothers Against Drunk Driving (MADD) and Remove Intoxicated Drivers (RID). The result has been a tremendous success. Fatalities have decreased by nearly 50 percent, from more than 20,000 persons in 1982 to just above 10,000 in 2018. Scores of thousands of people are alive today because of our efforts to persuade individuals to follow the admonition 'Don't Drink and Drive.' There is interest and hope in seeing that number diminish even further. Only time will tell." Larkin, *Driving While Stoned in Virginia*, *supra* note 267, at 4–5 (footnotes and punctuation omitted).
285. Emery N. Brown et al., *General Anesthesia and Altered States of Arousal: A Systems Neuroscience Analysis*, 34 ANNUAL REV. NEUROSCI. 601 (2011).
286. See Hamby, *supra* note 126 ("Mr. Rice went online and made an appointment with a doctor more than 2,500 miles from his California home whom he had never met. After a 30-minute video call, he received a prescription for a month's supply. 'I finally had an avenue to get pure medical-grade ketamine for cheap, sent to me over the mail,' he said. [¶] Not long ago, such an arrangement would have been illegal. Access to ketamine was tightly controlled by the Drug Enforcement Administration, which puts its risk of abuse one notch below that of opioids like oxycodone and fentanyl. While prescribing it for depression was allowed, patients needed to first meet in person with a doctor, and treatment was mostly limited to infusions in clinics. [¶] While many patients have benefited, the rapid growth of remote prescribing and at-home use of various drugs has outpaced the evidence that doing so is safe and effective. As the gap between medical treatment and online shopping has narrowed, already-thorny debates over the proper balance between availability and safety have become increasingly urgent. [¶] The ketamine boom is a particularly fraught case study of this new reality because of the drug's powerful effects and the vulnerable patients drawn to it: typically those with severe depression or other mental health conditions who have not responded to traditional therapies. The shift away from clinics has led many patients to take the drug more frequently and for longer periods of time—multiple times a week, even daily in some cases, and for months or years—despite scant research on safety.... With the rule changes in 2020, the at-home ketamine industry appeared practically overnight. [¶] Tech start-ups and individual doctors began offering medical services online, and so-called compounding pharmacies, which can make variations of approved drugs, found a market for tablet and lozenge versions of ketamine, normally manufactured as a liquid and distributed in vials:").
287. See, e.g., Freedman, *supra* note 142, at 2389 (noting that "ketamine is also widely used recreationally") (footnote omitted); see *supra* text accompanying notes 29–33 & 37–41.
288. See *supra* notes 239–40 and accompanying text.
289. See, e.g., FDA PSYCHEDELIC GUIDANCE, *supra* note 95, at 10.
290. Charles S. Grob, *Introduction: Hallucinogens Revisited*, in HALLUCINOGENS: A READER 1, 5 (Charles S. Grob ed. 2002).
291. *Id.* at 10.
292. *Id.*
293. *Id.*
294. OFF. OF NAT'L DRUG CONTROL POL'Y, NATIONAL DRUG CONTROL STRATEGY 2010, at 23 (2010).
295. For a suggested list of steps that the different levels of government can take, see, for example, Larkin, *Driving While Stoned in Virginia*, *supra* note 267, at 17–23.
296. POLLAN, *supra* note 72, at 382.



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