

VIEWPOINT

Two Models of Legalization of Psychedelic Substances Reasons for Concern

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In 1973, the federal government classified psychedelics as schedule I substances, rendering possession illegal, even for research purposes except under tightly regulated circumstances. Although these restrictions have hindered research on the therapeutic uses of psychedelics for decades, recent studies have brought increasing attention and enthusiasm to the potential benefits of psychedelic treatment.¹ Accompanying this revival of psychedelic research have been initiatives by states and localities to legalize psychedelic possession and use. Two of the most ambitious measures, in Oregon and California, take different paths to legalization. This Viewpoint reviews these initiatives and the concerns they raise by looking to the cautionary precedents involving the legalization and commercialization of other controlled substances.

Models of Psychedelic Legalization

Oregon became the first state to legalize broad clinical use of psilocybin, a schedule I psychedelic, through a November 2020 ballot initiative, the Oregon Psilocybin Services Act. The new law charged the Oregon Health Authority (OHA) with implementing clinical psilocybin regulation and licensure for treatment by the end of 2022. To guide the OHA in doing so, it created the Oregon Psilocybin Advisory Board, with members from psychology, allopathic and naturopathic medicine, public health, and other professions. Oregon appears to be expecting the federal government to ignore psilocybin use under the new law, as it has in states that have legalized the possession of marijuana, which is another schedule I drug.

In contrast, California Senate bill 519 would make California the first state to legalize the possession, personal use, and noncommercial sharing of psychedelics by adults, although similar local ordinances already have been adopted in Denver, Colorado; Oakland, California; Ann Arbor, Michigan; and Cambridge, Massachusetts. The bill was passed by the California Senate in June 2021 and, as of July 12, 2021, awaits action in the California Assembly. The bill also requires the state's Department of Public Health to study and report on approaches "to promote safe and equitable access...in permitted legal contexts." Should it fail to pass the Assembly, a 2022 ballot initiative with similar goals is being prepared.

Potential Benefits and Unknown Risks of Psychedelic Agents

Psychedelic research is still preliminary in many ways, although some studies have shown promising effects on depression, suicidality, substance use, and posttraumatic stress disorder (PTSD).¹ In a phase 2 clinical trial of 59 selected patients, there was no significant differ-

ence between psilocybin and escitalopram for treating depressive symptoms.² In a phase 3 trial involving 91 patients, 3,4-methylenedioxymethamphetamine (MDMA) was more effective than placebo for treating PTSD symptoms ($d = 0.91$).³ However, most of the literature on psychedelics has been limited by small sample sizes, difficulties with blinding given the subjective effects of psychedelics, and exclusion of participants with comorbidities, histories of drug use, and personal or family histories of psychotic disorders.¹⁻³ The extent to which findings like these may generalize to larger and more representative patient samples is unknown.

Serotonergic psychedelics, such as psilocybin, must be distinguished from other substances that are also sometimes called psychedelics and included in these legalization measures, such as the entactogen (ie, a compound that creates a sense of empathy and emotional connection) MDMA. The neurobiological mechanisms of neither class are fully understood, although according to many investigators the "mystical experiences" are critical to the clinical benefits of serotonergic psychedelics and empathetic effects to those of MDMA.¹

More importantly, current evidence for the risk profiles of these classes is notably different. The epidemiology and acute toxic effects of MDMA, including hyperthermia, hypertension, seizure, arrhythmia, and psychosis, have long been subject to careful study,⁴ enabling an evidence-based discussion of the risks of their use. In contrast, even though serotonergic psychedelics appear to have low abuse potential, their risks outside carefully controlled trials are not well understood. Early case reports of psychedelics precipitating psychotic episodes have led to understandable concern about their effects on people predisposed to psychotic disorders. The few large-scale surveys focusing on serotonergic psychedelics obtained illicitly offer conflicting guidance on this and other risks.

A study of 1993 psilocybin users who experienced "bad trips" reported that 62% characterized them as among the 10 most "challenging" experiences in their lives, 10.7% reported having put themselves or others at physical risk, and 2.6% had become physically violent.⁵ Ten percent of respondents reported symptoms lasting more than 1 year, with a small number of cases consistent with "enduring" psychosis (rather than substance-induced psychosis, which is, by definition, transient).⁵ Yet, other studies have suggested that history of psychedelic use was associated with decreased suicidality and distress⁶ and found no relationship between lifetime psychedelic use and current psychotic or other symptoms,⁷ although the incidence of transient, psychedelic-induced psychosis is uncertain.

The Diverse Roots of Psychedelic Advocacy

Despite the preliminary nature of the scientific evidence, the push for legalization of psychedelics is driven by the confluence of at least 4 factors. First is popular media, which have encouraged remarkable public enthusiasm about psychedelics, perhaps beyond that warranted by the current state of evidence. Second is the growing concern about the adverse effects of the criminalization of substance use, including high rates of incarceration in marginalized communities. These first 2 have led to a third: funding from a small number of wealthy enthusiasts in support of legalization of psychedelic substances. The fourth factor is the prospect of commercialization and resulting tax revenue. Venture capital firms and other investor-driven companies see opportunities to develop treatments and build clinics to profit from popular interest in psychedelics. State legislators have perceived that legalization of psychedelic substances, along with drugs such as cannabis, is a potential, easily tapped source of revenue for their cash-strapped states.

Although both therapeutic potential and positive effects of decriminalization are important considerations, advocates tend to give limited attention to countervailing concerns. Yet, if legalization is followed by commercialization, with psychedelic shops proliferating (like the cannabis boutiques that have opened in cities where that drug has been legalized), vulnerable populations may have unprecedented access to these substances. Moreover, the contribution of psychedelics to the criminalization and incarceration of Black individuals and other disenfranchised groups is not entirely clear; it may be several orders of magnitude less than that of other criminalized substances, such as cocaine and cannabis.

Lessons From Legalization and Commercialization of Drugs

Cannabis legalization offers an instructive analogy to the extraclinical legalization of psychedelics proposed in California. As with psychedelics, commercial interests encourage the perception that marijuana poses less psychiatric risk and offers greater benefit than the evidence suggests. Concerns about decriminalization are also critical to cannabis legalization efforts, and perhaps are more warranted than for psychedelics.

Although the results of cannabis legalization are debated, they are, at best, mixed. Benefits of decriminalization are clearly robust given the disproportionate frequency of incarceration for cannabis possession among disenfranchised groups, and other benefits in-

clude relief from specific types of pain. However, in states that have legalized cannabis, cannabis use disorder increased by 25% in people aged 12 to 17 years from 2008 to 2016 and by 36% in those older than aged 26 years.⁸ This may increase as commercialization progresses. For persons who use cannabis, use for self-medication, losses in social functioning, impaired driving, and psychiatric comorbidities have all increased with legalization.⁹ Perhaps most concerning, strong correlations between legalization and increasing prevalence of psychosis and consequent hospitalization have been reported. In Portugal, which decriminalized cannabis use in 2001, hospitalization in public hospitals for psychotic disorders increased from 24 in 2001 to 588 in 2015, and the proportion of patients with concomitant cannabis use disorder rose from 0.87% to 10.60%.¹⁰

Alternatively, even with strictly clinical use, as proposed for psilocybin in Oregon, non-evidence-based marketing may supplant evidence-based practice. As with the proliferation of for-profit chains of ketamine clinics, some firms now envision networks of psychedelic clinics for indications beyond treatment of depression. Investigative reports suggest that many ketamine clinics fail to screen patients properly, offer ketamine for indications and at doses not supported by appropriate evidence, lack a psychiatrist or other mental health professional on staff, and promote their services with claims far exceeding the evidence base. Because ketamine was already approved for use as an anesthetic, its off-label use is unregulated, in contrast to the US Food and Drug Administration Risk Evaluation and Mitigation Strategies required for the administration of esketamine, which is an intranasal formulation of ketamine.

Due Care in Psychedelic Legalization

The promise of therapeutic benefit from psychedelics is appealing, but overly rapid legalization and commercialization may short-circuit prudent legal reforms. There are other ways of accomplishing some of the goals of legalization while limiting the risks, such as deprioritizing enforcement of laws against psychedelic possession (as some cities have already done). Yet, the current debate creates a sense of urgency for decriminalization and a promise of solving a mental health "crisis" that may obscure potential harms of rapid implementation, largely unknown but potentially foreshadowed by prior experience. Slowing the rush to legalization of psychedelics to clarify the evidence, giving policy makers and the public better information, and to develop careful regulatory policy would be wise.

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