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PSYCHEDELICS, PSYCHOSOCIAL SUPPORT, AND PSYCHOTHERAPY: WHY IT MATTERS FOR THE LAW, ETHICS, AND BUSINESS OF MEDICAL PSYCHEDELIC USE

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INTRODUCTION

We may be on the cusp of a sea change in the relationship of psychedelic substances (hereinafter "psychedelics")[1] and the modern medical-industrial complex and clinical practice for certain disorders and medical needs. For example, we have seen promising results from a recent Phase III clinical trial for 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for moderate to severe post-traumatic stress disorder (PTSD).[2] Further, a Phase II clinical trial testing the use of psilocybin with psychological support for major depressive disorder has also had promising results.[3] Although in August 2024, the Federal Drug Administration (FDA) issued to Lykos Therapeutics ("Lykos"), a pharmaceutical company that developed out of the 501(c)(3) nonprofit Multidisciplinary Association for Psychedelic Studies (MAPS), a "complete response letter" rejecting the company's application

1. "Psychedelics" are a heterogenous set of substances that include naturally occurring fungi and plants that have been part of the healing and religious practice of Indigenous communities for millennia and some that were the result of synthesis by chemists in the early 20th century. *See, e.g.*, Mason Marks, I. Glenn Cohen, Jonathan Perez-Reyzin & David Angelatos, *Microdosing Psychedelics Under Local, State, and Federal Law*, 103 B.U. L. REV. 573, 576 (2023).

2. *See* Jennifer M. Mitchell, Marcela Ot'alora G., Bessel van der Kolkm Scott Shannon, Michael Bogenschutz, Yevgeniy Gelfand, Casey Paleos, Christopher R. Nicholas, Sylvestre Quevedo, Brooke Balliett, Scott Hamilton, Michael Mithoefer, Sarah Kleiman, Kelly Parker-Guilbert, Keren Tzarfaty, Charlotte Harrison, Alberdina de Boer, Rick Roblin, Berra Yazar-Klosinski, Charlotte Harrisoin & Berra Yazar-Klosinski, *MDMA-Assisted Therapy for Moderate to Severe PTSD: A Randomized, Placebo-Controlled Phase 3 Trial*, 29 NAT. MED. 2473 (2023).

3. *See* Charles L. Raison, Gerard Sanacora, Joshua Woolley, Keith Heinzerling, Boardie W. Dunlop, Randall T. Brown, Rishi Kakar, Michael Hassman, Rupal Trivedi, Reid Robison, Natalie Gukasyan, Sandeep M. Nayak, Xiaojue Hu, Kelley C. O'Donnell, Benjamin Kelmendi, Jordan Sloshower, Andrew D. Penn, Ellen Bradely, Daniel Kelly, Tanja Mletzko, Christopher R. Nicholas, Paul R. Hutson, Gary Tarpley, Malynn Utzinger, Kelsey Lenoch, Kasia Warchol, Theraysa Gapasin, Mike C. Davis, Courtney Nelson-Douthit, Steffanie Wilson, Carrie Brown, William Linton, Matthew W. Johnson, Stephen Ross & Roland R. Griffiths, *Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial*, 330 JAMA 843 (2023). It is important to note that *Nature Medicine* has retracted *other* papers that include members of the team behind the paper referenced above who were authors affiliated with a pharmaceutical company, because the journal was "informed of protocol violations amounting to unethical conduct at the MP4 study site by researchers associated with this project" and "[t]he authors have subsequently confirmed that they were aware of these violations at the time of submission of this article, but did not disclose this information to the journal or remove data generated by this site from their analysis," as well as a view that "the authors also did not fully declare a potential competing interest." *Retraction Note*, SPRINGER LINK (Aug. 10, 2024), https://link.springer.com/article/10.1007/s00213-024-06665-y [https://perma.cc/7R5L-282C] (retracting Lisa Jerome, Allison A. Feduccia, Julie B. Wang, Scott Hamilton, Berra Yazar-Klosinski, Amy Emerson, Michael C. Mithoefer & Rick Doblin, 237 PSYCHOPHARMACOLOGY 2485 (2020)). The reference to unethical conduct appears to be a reference to "an unlicensed Canadian therapist who took part in the trial engaged in a sexual relationship with a participant after the conclusion of the trial's dosing sessions." Andrew Jacobs, *Three Studies of MDMA Treatment Retracted by Scientific Journal*, N.Y. TIMES (Aug. 12, 2024), https://www.nytimes.com/2024/08/12/health/mdma-ptsd-retractions.html [https://perma.cc/MV9D-HGEF].

for approval for MDMA for PTSD after a contentious meeting for the Psychopharmacologic Drugs Advisory Committee (the "Advisory Committee").[4] It is possible that the company will be able to collect and submit new data to achieve approval in the future and certainly several other companies are pursuing approval for other psychedelics for other indications.[5] Although most of the public discourse has centered on *whether* a psychedelic will enter clinical practice with approval for medical use, this Essay will discuss *how* that medical use will be described, understood, and implemented.

Specifically, I am interested in contrasting the legal and ethical ramifications regarding psychedelics as drug therapy versus their use as a part of psychotherapy. The former approach would treat psilocybin, MDMA, or other psychedelics like other prescription drugs such as atorvastatin calcium (brand name LIPITOR®),[6] used to reduce the risk of myocardial infarction (heart attack), or fluoxetine (brand name PROZAC®),[7] used to treat major depressive disorder (among other health conditions).[8] The latter approach would conceptualize psychedelics' role as facilitating or enhancing psychotherapy.[9] To put it more crudely, the key difference from a regulatory, legal, and ethical perspective is whether we think of psychedelic therapeutics as something a patient is prescribed to take with some support from health professionals to ensure safety or as something that is administered to them as part of a more encompassing psychotherapeutic process. As I explain below, available regulatory options fall along a continuum with these alternatives as key poles on either end.[10]

A recent piece in *Lancet Psychiatry*, authored by a team led by Professor Gerhard Gründer, captures these dichotomous approaches by writing on one view that dates back to the 1950s:

> [T]herapy with psychedelics has been conceptualised as psychedelic-assisted psychotherapy—ie, a form of psychotherapy that uses the profound biological effects of this class of substances as a catalyst for changing thinking, emotions, and behaviour. In this view, the psychotherapy component of the treatment is considered as being of the utmost importance for both the safety and efficacy of the therapy. This

4. *See* Olivia Goldhill & Meghana Keshavan, *FDA Rejects MDMA as a Psychedelic Treatment for PTSD*, STAT NEWS (Aug. 9, 2024), https://www.statnews.com/2024/08/09/mdma-fda-rejection-of-ptsd-treatment-lykos-psychedelic/ [https://perma.cc/6MTL-G8S2].

5. *See* Kai Kupferschmidt, *FDA Rejected MDMA-Assisted PTSD Therapy. Other Psychedelics Firms Intend to Avoid That Fate*, SCIENCE (Aug. 12, 2024, 9:00 AM), https://www.science.org/content/article/fda-rejected-mdma-assisted-ptsd-therapy-other-psychedelics-firms-intend-avoid-fate [https://perma.cc/3U53-X8R4].

6. *See* FDA, LIPITOR LABEL (2019), https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020702s073lbl.pdf [https://perma.cc/X76U-VTXC]. This approved label also covers other conditions. *See id.*

7. *See* FDA, PROZAC LABEL (2017), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018936s108lbl.pdf [https://perma.cc/U8XV-3UF6]. This approved label also covers other conditions. *See id.*

8. *See infra* Part I.A.

9. *See infra* Part I.B.

10. *See infra* Part I.

> conceptualisation has been challenged by the idea that the latest clinical studies suggest that the potential therapeutic effects of psychedelics must be attributed solely to the substance itself, with no role for psychotherapy. Here, accompaniment by therapists is understood as mere psychological support, to maintain the safety of the substance administration.[11]

This topic is an active area of commercial debate with companies almost literally making "bet the company" assumptions on what the regulatory paradigm will look like. Indeed, a pugnacious statement in an interview of one of the most famous pioneers in this field, Rick Doblin, former founder and board member of Lykos, following the FDA's decision in the Lykos matter, captured the crucial question well:

> My whole idea was that Lykos would operate as a drug and therapy company. Now, Lykos is still figuring out if it's just a drug company, or still a drug and therapy company.
>
> What we're seeing in the psychedelics field—and I think the for-profit companies are going to interpret this from the FDA decision—is that they should move away from therapy. That's not what's best for patients.[12]

This Essay proceeds as follow. Part I briefly describes how vociferous this debate has become among advocates for the medical use of psychedelics. Part II discusses why this choice matters, legally and ethically. This includes a discussion of the potential FDA approval process for psychedelics, implications for cost and access (including insurance), what it might mean for professionalization and licensure, and the future of supported adult use frameworks we have seen in states like Oregon.

I. THE EMERGING DEBATE ABOUT THE ROLE OF PSYCHOTHERAPY IN THE MEDICAL USE OF PSYCHEDELICS

As we approach potential FDA approval of a psychedelic for medical use, stakeholders, who are all proponents of FDA approval, are battling over what that approval should look like, especially concerning the role psychotherapy should play in the therapeutic-use paradigm. For outside observers, perhaps the most surprising thing is just how nasty the rhetoric in this debate has become.

A. Psychedelics as Drug Therapy

A major shot across the bow came in July 2023 in a commentary in the *American Journal of Psychiatry* entitled "Must Psilocybin Always 'Assist

11. Gerhard Gründer, Manuela Brand, Lea J. Mertens, Henrik Jungaberle, Laura Kärtner, Dennis J. Scharf, Moritz Spangemacher & Max Wolff, *Treatment with Psychedelics Is Psychotherapy: Beyond Reductionism*, 11 LANCET PSYCH. 231, 231 (2023).

12. Meghana Keshavan, *Rick Doblin, "Unleashed," Blasts FDA over Lykos Drug Rejection and Turns to Global Push for MDMA Therapy*, STAT NEWS (Aug. 17, 2024), https://www.statnews.com/2024/08/17/mdma-psychedelics-rick-doblin-lykos-exit/ [https://perma.cc/JDC5-3ZP7].

Psychotherapy'?" (the "Goodwin article").[13] Its authors include the cofounder and the chief medical officer of Compass Pathways, a company pursuing FDA approval of a proprietary synthetic psilocybin formulation. Although ordinarily it might seem strange to give a single article so much attention, that attention seems warranted because the authors represent a company with one of the largest presences in this industry.

The article begins by attacking the terms "psychedelic-assisted psychotherapy" or "psychedelic-assisted therapy," suggesting a lack of clarity as to what these terms describe.[14] It takes as its starting point an account of "psychedelic-assisted therapy" (PAT) offered by a European organization that claimed that "the fundamental therapeutic benefit . . . comes from the combination of psychedelic medicine and therapy," that "[t]he drug is a catalyst for treatment, not a treatment in itself," and that the "psychedelics' novel therapeutic value stems from their role as enhancements to a psychotherapeutic process, grounded in a relationship-centered approach, that views mental health through a biopsychosocial lens."[15]

Guy M. Goodwin and the other authors criticize this account for evincing an "odd dualism," noting that the "drug as a medication presumably works on the brain (as a 'catalyst'), but there is a separate psychotherapy that it facilitates," and arguing that "there is no evidence that the conditions being targeted by psychedelics (severe depression, posttraumatic stress disorder (PTSD), and substance use disorders) are effectively treated by nondirective counseling."[16] The authors then argue that "the psychological support provided in recent studies of psilocybin is primarily directed to safety—specifically, the preparation and safeguarding of vulnerable people who are submitting to a potentially disorienting experience," and that patients in the study "do not typically receive evidence-based psychotherapy as it is usually understood."[17] Indeed, one sees how the authors are setting up an option in which psychotherapists are *not* (or very minimally) involved, given they state that "[s]taff with therapy backgrounds may be an excellent choice of personnel to provide the necessary and essential support" although they acknowledge that "it is an open question how far their efforts enhance efficacy rather than simply ensuring, as is intended, psychological and physical safety."[18]

After reviewing some of the history and recent studies that have been reported, Goodwin and the other authors then sketch out what "psychological support," the model they endorse, would look like and try to contextualize it

13. Guy M. Goodwin, Ekaterina Malievskaia, Gregory A. Fonzo & Charles B. Nemeroff, *Must Psilocybin Always "Assist Psychotherapy"?*, 181 AM. J. PSYCH. 20, 20 (2024).

14. *Id.*

15. *Id.* (quoting *Preparing Europe for Novel Psychedelic-Assisted Therapies: PAREA Launch*, PSYCHEDELIC ACCESS & RSCH. EUROPEAN ALIGNMENT, https://parea.eu/launch [https://perma.cc/4F3H-2B6L] (last visited Oct. 12, 2024)).

16. *Id.*

17. *Id.*

18. *Id.*

as not very different from chemotherapy or other, as I would say, "ordinary," medical interventions.[19] They write: "Preparation is the key function of the sessions leading to drug administration," asking "[w]hy would you not prepare a naive patient for exposure to a drug that can produce an extreme emotional experience, both positive and negative?" and "as a patient, how could you not want the person sitting with you in these circumstances to be sympathetic and supportive?"[20] They acknowledge that "[h]ow much the timing, content, and intensity of this preparation matter remains open for systematic inquiry," and that "for the most important studies of psilocybin in major depression, the time devoted to preparation could be as long as 8 hours and as short as 2 hours."[21] They note that "[o]n the day of administration, safeguarding requires that there be a responsible person present" and "[i]t has proved possible to employ a single individual or even a group setting."[22] They argue that "[t]his is analogous to the requirements for support of other medical procedures, such as cancer chemotherapy, but it is obviously made more complicated by the change in consciousness and the potential for abuse of the patient in an altered state."[23] They note that in the company's "COMP 001 trial, the therapist was required to remain present and available for support but explicitly to refrain from active guiding or prolonged discussions," that "[i]f the participant became active or restless, the therapist was to encourage direction of their attention inward," and observe that "[t]he core principle was to help participants maintain attention on the experience of the present moment and be open to a maximally immersive drug experience.[24]

They then argue that the "data on the impact of integration or debriefing after the psychedelic experience remain scant" in the recent reported studies, suggesting there is some evidence that "the dose-related reduction in depressive symptoms was fully developed in responders on the day following treatment . . . and before any integration had taken place," and that there is "little room for inference from existing studies of a major effect of integration, the element of the total treatment that most obviously entails patient/therapist interaction."[25]

They posit that the evidence for psychotherapy focused on integration[26] has not been made, writing:

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19. *Id.*
20. *Id.* at 21.
21. *Id.*
22. *Id.*
23. *Id.*
24. *Id.*
25. *Id.*
26. Although there may be some disagreements as to what exactly "integration" means in the psychedelic therapy context, a good working definition is presented by Dr. Collin. M. Reiff and coauthors who write that "[a]fter the medication session, during the integration sessions, the therapists work with the patient to interpret the content of the psychedelic experience into meaningful long-term change through identifying insights or interpreting thoughts or ideas that arose during the psychedelic session." Collin M. Reiff, Elon E. Richman, Charles B. Nemeroff, Linda L. Carpenter, Alik S. Widge, Carolyn I. Rodriguez, Ned H. Kalin, William

> The role of integration, and indeed of additional psychotherapy of other kinds, is, in our opinion, still an open and very interesting question. It may be important, again from a safety perspective, to assess patients for unusual persistent beliefs or the impulsive intention to make drastic changes in their lives (for example, in their wills or in other major financial decisions). In addition, the experience is so unusual that psychedelically naive patients just want to talk to someone who has seen others in this state before. It is the assumption of many therapists that integration is crucial to efficacy. The complexity they see in the process implies much more work than is possible in two integration sessions. But, alternatively, a more systematic use of behavioral activation or cognitive-behavioral therapy (CBT) in the time immediately after the psychedelic experience might capitalize on the fertile state [of the mind post administration].[27]

But this same paragraph ends on a very different note, observing:

> However, their incremental benefit is currently unclear because of a lack of necessary comparators. Supported by rigorous randomized clinical trials, they offer a glimpse into how psilocybin may fit into conventional evidence-based treatment programs once its efficacy and safety have been confirmed at scale for regulatory approval. They are not comparable with the approach employed so far to *achieve* regulatory approval.[28]

Put less politely, and only a tad cheekily, the authors are essentially saying, "Do all the psychotherapeutic research you want, but make sure to keep it separate from my drug approval!" Indeed, this subtext comes closer to text earlier in the paper where the authors write:

> It is important to get this right, because regulatory bodies are asked to approve drugs with a defined efficacy and safety, not psychotherapies. Indeed, the drug effect can only be established unambiguously if psychological support is available largely to ensure safety and is applied in a stereotyped way, whatever the drug dose. Any complex interaction with a therapist during the active drug experience clearly complicates interpretation of treatment outcomes; therapist expectations could create conditions ripe for mutual unblinding and the amplification of demand characteristics. Additionally, the harms that can result from the interactions between therapists and patients during a psychedelic experience may not be fully appreciated. Unregulated psychotherapy practice regularly leads to ethical violations. The risk that such practice could become the natural partner in "psychedelic-assisted psychotherapy" has been highlighted recently. There is therefore nothing to be gained by exaggerating the role of psychotherapy in deriving benefit from the psychedelic experience.[29]

Notice the several moves in the argument here: the suggestion that the severing of the psychotherapy and the drug is *necessary* because of the needs of regulators who are considering approval, that the role of the

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M. McDonald & the Work Group on Biomakers and Novel Treatments, *Psychedelics and Psychedelic-Assisted Psychotherapy*, 177 AM. J. PSYCHIATRY 391, 402 (2020).

27. Goodwin, *supra* note 13, at 21–22.

28. *Id.* at 23.

29. *Id.* at 20.

psychotherapist is at risk of being "exaggerat[ed]" (i.e., that the drug is doing all the work), and that instead of being *helpful* or improving safety, psychotherapists and their involvement will actually lead to "ethical violations."[30]

The authors cite to a JAMA Psychiatry Viewpoint piece from March 2023 that references a case in a clinical trial where a therapist was recorded "pinning down a participant, cuddling and kissing her, and physically overpowering her" along with other incidents of "sexual exploitation."[31] The Viewpoint piece argues that

> [i]n PAT, patients are under the influence of substances that may enhance suggestibility and impair capacity for consent and withdrawal (which is also restricted by protocol), potentially increasing overcompliance with therapist suggestions. The use of conventional psychotherapy approaches, which require active, ongoing, and dynamic consent, poses unique risks and problems. Even psychotherapy practices with an existing evidence base need to be reevaluated for safety and efficacy in PAT.[32]

The Viewpoint piece concludes that "the psychotherapy protocols that accompany psychedelic administration [are] an understudied and undertheorized source of preventable risk in PAT" and argues that "[i]f the field fails to attend to this gap, anticipated regulatory approvals will mandate that patients undergo untested and controversial psychotherapy protocols alongside the use of psychedelics," which "would expose future patients to unnecessary risk and put clinicians at risk of malpractice if the SAEs [(serious adverse events)] reported herein were to occur in their clinical practices."[33]

At the same time, the authors do not unequivocally condemn a requirement that psychotherapy accompany use of psychedelic substances. Instead, they conclude that "researchers must undertake phenomenological research to better understand SAEs, and researchers without personal and financial conflicts of interest must conduct and evaluate research."[34]

B. In Defense of Psychedelic-Assisted Therapy

The Goodwin article stirred up a hornet's nest of responses. First came the responses in the same journal in the form of short letters. For example, an article written by Michael D. Alpert and his coauthors, who identified themselves as "investigators on trials of MDMA-assisted therapy (MDMA-AT)," expressed their "concern[]" that "Goodwin et al. are charting a course that will jeopardize the welfare of vulnerable patients, and the viability of this nascent field" and critiqued them for "ignor[ing] the

30. *See id.*

31. Sarah McNamee, Neşe Devenot & Meaghan Buisson, *Studying Harms Is Key to Improving Psychedelic-Assisted Therapy—Participants Call for Changes to Research Landscape*, 80 JAMA PSYCHIATRY 411, 411–12 (2023).

32. *Id.* at 411.

33. *Id.* at 412.

34. *Id.*

extensive preparation, support, and integration—provided by very experienced psychotherapists—that define the rigorously designed psilocybin trials" they cite.[35] They argue that "the subjective experience of the participants—both in ordinary and non-ordinary states—is paramount for treatment effect, and that 'drug effect per se' is likely illusory, given the interaction between the set, setting, and the experience-amplifying effects of these drugs."[36] Although they acknowledge that psychotherapy increases initial treatment costs, they claim that "evidence shows it can be cost saving overall" and draw comparisons to surgery, dialysis, and chemotherapy.[37] However, they argue that this cost concern evinces a "double standard for mental health care."[38]

Eduardo Ekman Schenberg and coauthors push back on the claim that what occurred in the Goodwin article's trial (the "Compass trial") was not PAT.[39] They also suggest that it "seems reasonable to speculate that higher rates of serious adverse events in" some of the groups receiving psilocybin in the trial "might have been mitigated with greater emphasis on relational elements during preparation and integration—rather than simply 'psychological support.'"[40] Finally, they allege "potential biases and conflicts of interest involved in developing a proprietary synthetic formulation of psilocybin, which . . . could potentially influence efforts to more easily bring a drug to market by downplaying the role of therapy."[41]

Dr. Kelley C. O'Donnell and coauthors criticize the Goodwin article for attributing "long-term antidepressant benefits to the 'psychedelic experience,' a conclusion that cannot be drawn when the intervention assessed was psilocybin [assisted therapy], with no treatment arm receiving psilocybin alone."[42] They chide Goodwin and his coauthors for failing to appreciate data showing that "greater therapeutic alliance before the psychedelic experience predicted greater emotional breakthrough."[43] They

35. Michael D. Alpert, Kelley C. O'Donnell, Casey A. Paleos, Evan Sola, Christopher S. Stauffer, Anne C. Wagner, Christopher R. Nicholas & Michael C. Mithoefer, *Psychotherapy in Psychedelic Treatment: Safe, Evidence-Based, and Necessary*, 181 AM. J. PSYCH. 76, 77 (2024).

36. *Id.*; *see also* Garrett Marie Deckel, Lauren A. Lepow & Jeffrey Gruss, *"Psychedelic Assisted Therapy" Must Not Be Retired*, 181 AM. J. PSYCH. 77, 77–78 (2024) (claiming the Goodwin article is hindered by "a fundamental misunderstanding of PAT and the nature of the interaction between psychedelic drug and context ('setting')" because "[d]rug-therapy interactions are reciprocal and iterative, yielding mutual and inseparable effects").

37. *Id.*

38. *Id.*

39. Eduardo Ekman Schenberg, Franklin King, João Eusébio da Fonseca & Leor Roseman, *Is Poorly Assisted Psilocybin Treatment an Increasing Risk?*, 181 AM. J. PSYCH. 75, 76 (2024).

40. *Id.*

41. *Id.*

42. Kelley C. O'Donnell, Brian T. Anderson, Frederick S. Barrett, Michael P. Bogenschutz, Charles S. Grob, Peter S. Hendricks, Benjamin Kelmendi, Sandeep M. Nayak, Christopher R. Nicholas, Casey A. Paleos, Christopher S. Stauffer & Natalie Gukasyan, *Misinterpretations and Omissions: A Critical Response to Goodwin and Colleagues' Commentary on Psilocybin-Assisted Therapy*, 181 AM. J. PSYCH. 74, 74 (2024).

43. *Id.*

also argue that many patients receiving "[PAT] in research settings seek additional support outside of study protocols, suggesting an unmet psychotherapeutic need" and express concern that a "push to further reduce psychotherapy in psychedelic treatment ignores this fact and could place patients at higher risk of adverse outcomes."[44] They argue that "the COMPASS trial provided less support than prior studies, and reported not only smaller and less durable effects relative to other completed trials of psilocybin for mood disorders" but also "three instances of suicidal behavior in participants receiving high dose psilocybin—the first time such outcomes were reported in a [PAT] trial."[45]

Professor Mitch Earleywine and his coauthors suggest that "perhaps some depressed clients could improve with psilocybin without psychotherapy, especially with appropriate social support and previous experience," but because "[o]nly data can answer this question," a clinical trial comparing groups with and without extensive psychotherapy is warranted.[46] They raise an ethical question as to whether "the thought of sending clinically depressed clients home after a session with little more than a scheduled follow-up might give many professionals pause," but they do not outright reject the idea.[47]

In a longer response, Professor Gründer and coauthors, writing in *The Lancet Psychiatry*, argue that the Goodwin article's views represent "an outdated reductionist dualism that is impeding progress in psychiatric therapy research" because "the effects of treatment with a psychotropic drug can never be completely—or even partially—separated from the effects of the psychosocial environment in which it is applied" and this "context dependence is particularly evident for psychedelic drugs, as some of their psychological and neurobiological effects can be characterized as increased sensitivity and adaptability to context."[48] Alluding to the regulatory review of the clinical trials, they argue that "it is naive to think that these effects could be controlled for simply by adding a placebo group to an experimental setup."[49]

Professor Gründer and his coauthors accept the distinction between psychological support and psychedelic therapy, characterizing the support approach as having three parts: "The first part is preparation, which usually takes 2–8 [hours] and serves to build trust and rapport, provide psychoeducation, and prepare for the psychedelic experience."[50] In the second part, "the dosing session, therapists are required to remain present and available for support but explicitly refrain from active guiding or prolonged

44. *Id.*
45. *Id.*
46. Mitch Earleywine, Joseph De Leo, Dinesh Bhayana, Bhavya Rajanna & Karen Scott, *Psilocybin Without Psychotherapy: A Cart Without a Horse?*, 181 AM. J. PSYCH. 78, 78 (2024). A similar sentiment is expressed by Dr. O'Donnell and her coauthors, see *supra* note 42, at 74 ("The psychological support required deserves rigorous empirical study, though the evidence suggests it plays an indispensable role. It is premature to suggest reducing it.").
47. Earleywine et al., *supra* note 46, at 78.
48. Gründer et al., *supra* note 11, at 231.
49. *Id.*
50. *Id.*

discussions."[51] Finally, "[i]n the third phase, usually one or two integration sessions are intended to support participants in deriving their own insights and solutions from the experience with the psychedelic."[52] In this phase "[t]herapists are advised to remain open and supportive, without active guiding," and they emphasize that "the explicit goal of psychological support is to provide and increase safety rather than to secure and facilitate efficacy, again implying that efficacy and safety are dimensions in drug treatments that can be separated from each other."[53]

But, they argue, this is not enough because of the context-dependent nature (set and setting) of the effects of psychedelics. The psychotherapy piece is essential because a "psychedelic session that is experienced as negative or a so-called horror trip under unfavourable conditions can potentially be experienced as helpful or cathartic in a well controlled therapeutic context that allows for a thorough processing of the experiences in the weeks and months after the psychedelic session."[54]

They claim that the therapy may not be necessary just for efficacy but even for the safety profile of psychedelics, writing: "[T]he suggestion by regulators that staff not involved in the post-session psychotherapeutic treatment of a patient should accompany psychedelic sessions could put the treatment at substantial risk."[55] They note that "[a]dverse childhood experiences (including emotional, physical, and sexual abuse, as well as neglect) are associated with later mental and physical disorders" and worry that "[u]nder the influence of a psychedelic, even minor interactions with other people can be experienced as vastly meaningful and of great impact."[56] They posit that "[i]f intentionally and skillfully accompanied, psychedelic states can provide an opportunity for facilitating new and clinically significant corrective experiences in human interaction that allow the relearning and alteration of existing maladaptive beliefs or schemas," but that "[n]eglect or ignorance of the importance of intentional, well informed, and long-term therapeutic interaction between a patient and therapist can cause great harm to patients, for example, by strengthening dysfunctional patterns or leading to retraumatisation."[57] For that reason they posit that the monitoring of sessions by a person who does not know a patient and is only meant to provide supportive care for their safety potentially endangers the therapeutic process"; that is, "[d]eclaring the effects of a therapy to be purely due to the drug itself by denying the importance of psychotherapeutic embedding does not make it a biological therapy, nor does it make it any safer."[58]

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51. *Id.*
52. *Id.*
53. *Id.* at 232.
54. *Id.*
55. *Id.*
56. *Id.*
57. *Id.*
58. *Id.* at 234.

Professor Gründer and his coauthors accordingly suggest that "there is an ethical imperative that psychedelic interventions should not be conducted outside an appropriate psychotherapeutic framework."[59] They think this directive is necessary to further "the common good and beneficial long-term outcomes, but [is] not necessarily compatible with the shorter-term financial interests of stakeholders," and urge regulators to push against "cost reductions where these could compromise the safety, efficacy, and ethical appropriateness of treatments."[60]

These authors argue that in the clinical trials used to support FDA approval of psychedelics, "[p]sychological support . . . appears not to be a mere safety measure but a form of psychotherapy—albeit a minimal one that, in many cases, probably cannot exploit the full potential of psychotherapy."[61]

Goodwin and his coauthors responded to these criticisms.[62] Although they do not claim that "nonspecific therapeutic elements such as therapeutic alliance, a healing setting/context . . . are irrelevant in contributing to therapeutic outcomes," they find their opponents' argument that the psychedelics "solely catalyze the therapeutic efficacy of nonspecific therapeutic factors to produce therapeutic outcomes is nonsensical and lacking in parsimony."[63] Goodwin and his coauthors push back on the idea that psychotherapy drives the results in their clinical trials, stating they "keenly await dismantling studies to test the drug and behavioral components as active ingredients," but "in the absence of such existing data, we do not believe it makes sense to attribute the therapeutic benefit primarily to an unspecified interaction of certain drug dosages and the behavioral intervention, as if the drug effects were a mystery."[64] Instead, they argue that "the more parsimonious explanation is that differences in drug dosage are driving differential therapeutic benefits" and point out that "[t]he COMP001 trial . . . gave identical psychological preparation and support to three groups who then received different doses of psilocybin," and argue the different outcomes "reflected the drug dose."[65]

Goodwin and his coauthors disagree with critic's characterizing their recommendation as being "to reduce psychological support," and argue that the "issue is whether psychological support is primarily about patient safety or efficacy," and "[f]or the moment, given the evidence, the reasonable deduction is that it facilitates patient safety and may assist optimal engagement with and subjective experience of the drug effects."[66] Instead, they claimed that their article "simply asked whether the terminology

59. *Id.* at 235.
60. *Id.*
61. *Id.* at 233.
62. *See generally* Guy M. Goodwin, Ekaterina Malievskaia, Gregory A. Fonzo & Charles B. Nemeroff, *Psychological Support for Psilocybin Treatment: Reply to Letters on Our Commentary*, 181 AM. J. PSYCH. 79 (2024).
63. *Id.* at 79.
64. *Id.*
65. *Id.* at 80.
66. *Id.*

(psychedelic-assisted psychotherapy) actually captured the processes currently at work in the reported trials with psilocybin."[67]

II. WHY DOES THIS DEBATE MATTER FOR LAW, ETHICS, AND REGULATORS?

Whether medical use of psychedelics is only (or mostly) safe and effective as a pure prescription drug therapy, like PROZAC® with some scaffolding of psychosocial support as well as monitored administration and monitored trip, or alternatively as part of a developed psychotherapy model, is an important question for medicine (although outside the scope of this Essay).[68] Underlying this question, though, is a still bigger one: What is it we are hoping the medical use of psychedelics will achieve, and how are we measuring *that*? If one begins by framing the question along the lines of "how does it perform in comparison to traditional antidepressant drugs already in the market in reducing the symptoms and criteria for major depressive disorder under the Diagnostic and Statistical Manual of Mental Disorders ('DSM-V-TR')?" or the equivalent question for PTSD, one is likely to go in a particular direction. If, instead, one frames the question as "how does it perform in enabling patients suffering from these disorders to make meaningful changes in their lives, leading them to a place of more fulfillment?" one is likely to go in quite a different direction. This Essay, however, intends to answer a smaller question: How does framing safe and effective use of psychedelics in a psychedelic-assisted therapy model, rather than one that emphasizes only psychosocial support, affect law and policy in the coming years? I examine four interconnected areas where the answer to this question will make a difference: (1) drug approval conditions, (2) business models, (3) cost, and (4) access.[69]

A. Why This Debate Matters for FDA Drug Approval

Although the initial application for FDA approval for MDMA to treat PTSD did not succeed, the sponsors may seek to submit new data in hopes of approval. In any event, we are likely to see an application soon for a patented psilocybin polymorph to treat major depressive disorder.

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67. *Id.*

68. I agree with many of the commentators above that without decomposing studies, such as clinical trials that unbundle the different types and levels of psychotherapeutic interaction, we will be unable to give an evidence-based answer to the question. Professor Mason Marks and I made a similar point in responding to the FDA's most recent guidance to the pharmaceutical industry in conducting clinical trials for psychedelics. *See* Mason Marks & I. Glenn Cohen, *How Should the FDA Evaluate Psychedelic Medicine?*, 389 NEW ENGL. J. MED. 1733, 1734 (2023) ("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. Peer support could be helpful and economical, as it is in outpatient OUD treatment. Researchers could study these questions, and the FDA should remain open-minded about revisiting this issue.").

69. Access in turn is connected to insurance reimbursement and the relationship between medicalized and nonmedicalized models of accessing psychedelics. *See infra* Part II.B and accompanying text.

1. The FDA's Attitude Toward Psychotherapy and Evaluation Thereof in This Context

The FDA's hearing for the Lykos application for MDMA repeatedly demonstrated the awkward fit between the FDA's understanding of its mandate and its competency to evaluate the effect of a drug in a clinical trial protocol that arguably mixed drug and psychotherapeutic interventions. For example, Dr. Tiffany Farchione, the Director of the Office of Neuroscience's Division of Psychiatry at the FDA, stated: "[The] FDA does not regulate the practice of psychotherapy, but it is possible to include some language about therapy in a label, and even as part of an indication statement."[70] That is, "[i]f another mode of therapy is necessary in order to achieve a therapeutic response, we can say that the drug is indicated for use only in conjunction with the other mode of therapy." By contrast, she continued, "here, the contribution of psychotherapy to the overall treatment effect observed in these clinical studies has not been characterized," in that "[a]ll of the treatment arms in all of the studies submitted included psychotherapy," and the "manualized therapy employed in this development program included therapeutic components that have been previously studied in people with PTSD, but there have been no rigorous studies directly comparing this particular manualized therapy to other psychotherapeutic approaches or to midomafetamine alone without psychotherapy."[71] She continued: "Nonetheless, with psychotherapy present in all treatment arms, the proposed paradigm of three midomafetamine medication sessions delivered over 4 months was superior to placebo for treatment of PTSD and remained superior to placebo at a long-term follow-up assessment," and intoned "[t]hat said, the observed benefit in the placebo arm was also maintained at follow-up, suggesting that the therapy did provide some benefit."[72] For these reasons, she concluded that "if this product were to be approved, we can't label it for use on its own, but we also don't have strong evidence that the therapy is necessary to the observed effect."[73]

For those like Professor Gründer and others discussed above, who view psychedelic's therapeutic value as assisting psychotherapy, the FDA's attitude creates something of a conundrum: the drug is useful in improving psychotherapy, but because the FDA understands itself as *not* regulating psychotherapy, its goal is, in lay terms, to "factor out" the very psychotherapy components it views as facilitating positive change. Factoring out makes sense based on a view of psychedelic efficacy that is psychotherapy-independent—psychotherapy as drug therapy—where one connects the taking of the drug to the outcome measure; it is in tension, if not directly contrary, to a view that the value of psychedelics is in assisting

70. FDA CTR. FOR DRUG EVALUATION & RSCH., PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING (PDAC) TUESDAY, JUNE 4, 2024, at 27 (2024), https://www.fda.gov/media/180703/download [https://perma.cc/W9GE-LCC4].

71. *Id.* at 27–28.

72. *Id.* at 28.

73. *Id.*

psychotherapy, for which one would want to measure how the psychotherapy modulates or is modulated by the substance.

Here, it is useful to distinguish two subtly different attitudes a regulator could have:

(1) "Show me the Value": If psychotherapy is an important part of the regulated "product" (scare quotes intentional), show its value with a study design that can separate out the effect from the drug versus the effect of the drug with psychotherapy, versus neither, and ideally compare multiple elements of the psychotherapy and/or multiple psychotherapies to determine what it is about the psychotherapy that does the work.[74]

(2) "Just the Drugs, Please!": Although in the real world, the FDA does not intend to *stop* people from using psychedelics as part of psychotherapy, that is just not something we as an agency care about or feel empowered/capable of looking at. For that reason, we want to be sure that the drug does what you say it does without the psychotherapy. At least give us that. Design your trials accordingly such that if you use psychotherapy, you can give us confidence it is not "doing the work" that produces the effect.

If you reread the quote from the FDA representative at the Advisory Committee meeting, you get some mix of these two related but different attitudes.[75] Is the concern that the sponsor did not adequately standardize the psychotherapeutic elements or design the trial in such a way that the agency can be confident these things add value, how much, and in what way (Show me the Value), or is the concern that those same failures stymie the agency's ability to determine what the drug-only effect is, which is all the agency cares about (Just the Drugs, Please)?[76] The more of the Advisory Committee meeting one listens to the more it seems like the latter. This mirrors the approach the FDA took in recent guidance on clinical trials involving psychedelics.[77] Far from requiring psychotherapy as a condition of approval of medical use of psychedelics, the FDA suggests it is trying to evaluate psychedelics *without* psychotherapy, noting that "[p]sychotherapeutic interventions have the potential to increase expectancy and performance biases" such that "[s]ponsors should plan to justify the inclusion of a

74. To make matters more complex, there is no reason to believe that the effect of psychotherapy is linear or unidirectional—it could be an inverted U-shape, for example, where psychedelics helps a patient's results with a certain number of hours of psychotherapy, hurts a patient for an additional number of hours, and helps again with even more hours. It could also be that some elements of psychotherapy are assisted and some are hampered by the psychedelics. And, of course, the causal arrow could flow in the opposite direction—that the psychedelics are "doing the work" and a certain amount or some elements of psychotherapy help while others hurt. There could be even more complex interactions!

75. FDA CTR. FOR DRUG EVALUATION & RSCH., *supra* note 70.

76. There were other similar exchanges in the Advisory Committee meeting that also seem to walk the line between the two attitudes. *See, e.g.*, *id.* at 92–93 (exchange between Professor Paul E. Holtzheimer, Advisory Committee Member, and Dr. Berra Yazar-Klosinski, of Lykos); *id*. at 151–53 (statement by David Millis of the FDA).

77. FDA, PSYCHEDELIC DRUGS: CONSIDERATIONS FOR CLINICAL INVESTIGATIONS GUIDANCE FOR INDUSTRY 9 (2023), https://www.fda.gov/media/169694/download [https://perma.cc/B5G5-VNVR].

psychotherapy component and describe any trial design elements intended to reduce potential bias or to quantify the contribution of psychotherapy to the overall treatment effect."[78]

A different way of stating the issue is whether the FDA is open to evaluating a treatment that requires or is designed to be used with a certain kind of psychotherapy—a drug plus psychotherapy combination? The FDA does, after all, have a well-developed set of processes for regulating what it calls "combination products"—products that "combine drugs, devices, and/or biological products."[79] But these combination products are combinations of things that it already regulates, rather than combining something it does regulate (drugs) with something it views itself as not regulating (psychotherapy).

The FDA's most telling statement indicating its reluctance to require anything to do with psychotherapy came from Dr. Farchione's response as to whether, if FDA approved the sponsor's drug, it would require "enrollment in [the sponsor's] therapy training program."[80] This response refers both to the drug and label approval, and to any potential Risk Evaluation and Mitigation Strategy (REMS), a drug-specific risk management plan.[81] Dr. Farchione stated:

> Well, the difficult thing, and something that you've just hit on very well, is that we don't regulate psychotherapy at all, so we don't really have any say in the design or the implementation of the particular therapy that is going to be used. We can say, generally, that this is something that would need to be administered in conjunction with a psychological intervention, but that's really the extent of what any labeling language would suggest. And even when it comes to the parameters of the REMS, those are focused on safety and monitoring, not on the intervention that would occur at the time.[82]

And when asked whether the FDA "would . . . have the ability to say, for example, that this therapy training program is not required," Dr. Farchione responded that the agency "wouldn't have any comment on that," although she acknowledged in response to a follow-up that the sponsor might itself impose such a requirement, "it wouldn't be a requirement that we [the FDA] would implement."[83]

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78. *Id.*

79. *Combination Products*, FDA, https://www.fda.gov/combination-products [https://perma.cc/WF92-RBT5] (last visited Oct. 12, 2024).

80. FDA CTR. FOR DRUG EVALUATION & RSCH., *supra* note 70, at 201.

81. *See infra* Part II.A.2.

82. FDA CTR. FOR DRUG EVALUATION & RSCH., *supra* note 70, at 201–02.

83. *Id.* at 202–03. Dr. Farchione, in my view, appropriately uses "would" not "could" in this space—indicating what the agency believes is appropriate or not. There is a separate question of whether the agency actually has the authority, under the law, to impose a requirement of a particular kind of therapy or therapy training program. This relates to the shibboleth that the FDA does not regulate the practice of medicine. The question of whether that is a completely true statement and also whether it matches the outer boundaries of what the FDA could do is complicated, entwined with issues regarding the scope of preemption of state law in this space. For good discussions of this issue, see Patricia J. Zettler,

Where does this leave things? Although, as discussed in Part I, there is an active and vociferous debate between those who have a model of psychedelics as drug therapy versus those who believe its therapeutic benefits come in assisting psychotherapy, the FDA does not seem as open to each possible model. The Lykos new drug application (NDA) and its underlying business model, discussed in further detail below,[84] can be fairly characterized as leaning toward the assisting psychotherapy model.[85] In the Advisory Committee hearing, the FDA appeared not only to push on the question of whether the sponsor had adequately characterized, measured, and controlled for the psychotherapeutic versus the drug effects, but suggested that it did not think it would ever consider approving a "product" (again, scare quotes) that required psychotherapy or had psychotherapy as an important element for safe and effective treatment with a psychedelic.[86] This, in and of itself, suggests only some kinds of approaches to psychedelics as therapy, and only some business models, will be compatible with FDA's review. As I discuss more fully below, this will deeply shape the future of incentives to seek drug approval, and whether FDA-approved psychedelics are used primarily in or outside psychotherapy.

2. REMS Accompanying an Approved Psychedelic

Besides the overall decision whether to approve a drug for a particular indication, Congress empowered the FDA to impose risk management plans as part of its approval process. The Food and Drug Administration Amendments Act of 2007[87] (FDAAA) gave the FDA authority to impose a Risk Evaluation and Mitigation Strategy, which it has done for about sixty drugs, including mifepristone, used for medication abortion.[88] Under the statute, the FDA works with a sponsor of a NDA to consider potential restrictions on the use of that drug based on six enumerated 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.

Pharmaceutical Federalism, 92 IND. L.J. 845 (2017); Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427 (2015); Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149 (2004).

84. *See infra* Part II.A.2.

85. *See supra* Part I.B.

86. *See supra* Part I.B.

87. Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 and 42 U.S.C.).

88. Peter Grossi & Daphne O'Connor, *FDA Preemption of Conflicting State Drug Regulation and the Looming Battle over Abortion Medications*, 10 J.L. & BIOSCIENCES 1, 6 (2023). For full disclosure, I have participated in an amicus brief in the mifepristone case, *FDA v. Alliance for Hippocratic Medicine*, 144 S. Ct. 1540, 1552 (2024) (concluding plaintiffs lack standing in their challenges to FDA's decisions regarding mifepristone), and have written about it in various venues.

> (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.[89]

The FDA is the one that initially determines whether a REMS is appropriate, at which point the NDA holder can propose a plan to the FDA, which the FDA reviews before issuing a REMS as a final agency action.[90] The FDA also must "periodically" reassess the REMS to ensure it is meeting the patient safety goals consistent with access and cost-effectiveness.[91] Under the same statutory authority, a REMS can also contain what are called:

> 'Elements to Assure Safe Use' (ETASU)[,] restricting use of a drug to providers who have special training, experience or certification; limiting pharmacy dispensation to those who likewise have special certification; limiting use to certain 'settings' such as hospitals; and/or mandating enhanced patient monitoring [but must determine] that such restrictions should not be 'unduly burdensome on patient access to the drug' and should 'to the extent practicable, minimize the burden on the health care delivery system'.[92]

Although most drugs do not have REMS, I foresee the FDA imposing REMS that arguably relate to therapy for some drugs that focus on mental health. For example, VIVITROL® is approved for "those being treated for alcohol dependence," and the label specifies that it "should be part of a comprehensive management program that includes psychosocial support."[93] SUBUTEX® is "indicated for the treatment of opioid dependence," and the label specifies that it "should be used as part of a complete treatment plan to include counseling and psychosocial support."[94]

It is quite possible that we will see a REMS with ETASU accompany psychedelic approval with requirements at least similar to what the FDA required for SUBUTEX® and similar products, which, at one point require that "each patient" is subject to "monitoring" for, among other things, "[a]ssessment of whether [each] patient is receiving the necessary psychosocial support" and "assessment of whether [each] patient is making adequate progress towards treatment goals."[95]

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89. 21 U.S.C. § 355-1(a)(1)(A)–(F).

90. *See id.* § 355-1(a)(2)(B), (f)(5), (h)(1).

91. *Id.*; Grossi & O'Connor, *supra* note 88, at 6–7.

92. Grossi & O'Connor, *supra* note 88, at 6 (citing 21 U.S.C. § 355-1(f)(3)(5)(A)(ii)–(B)(ii), (g)(2)(C)(ii)).

93. FDA, VIVITROL LABEL 1 (2010), https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s015lbl.pdf [https://perma.cc/XC77-WNLM].

94. FDA, SUBUTEX LABEL 3 (2011), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf [https://perma.cc/Q68P-X9BH].

95. FDA, BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS FOR OPIOID DEPENDENCE (BTOD), RISK EVALUATION AND MITIGATION STRATEGY (REMS) 5 (2017),

At the same time, this REMS language from other drugs is quite vague as to what is required as part of "counseling" or "psychosocial support." Although full-blown psychotherapy would in many cases qualify as sufficient, if this language is used, psychotherapy will not be required. Regardless of whether this is the all things considered right decision, I think this is the most likely direction for the FDA, not only because the June guidance hints in this direction, but because of the reticence regarding psychotherapy evinced by the agency in the Advisory Committee hearing discussed above.

In the materials submitted as part of the Advisory Committee process related to Lykos' MDMA approval, the FDA proposed a REMS to consist of an ETASU, "an implementation system and a timetable for submission of assessment."[96] The Agency's proposed REMS, including its ETASU, set out that "the drug can only be dispensed in certain healthcare settings, the drug be dispensed to patients with evidence or other documentation of safe-use conditions, each patient using the drug be subject to monitoring, and each patient using the drug be enrolled in a registry."[97] The FDA wrote that the "proposed REMS goal is to mitigate the risks of serious harm resulting from patient impairment from midomafetamine administration by ensuring that patients are managed in a medically supervised healthcare setting during and after midomafetamine administration."[98] It stated that "[t]he serious harms of interest include but are not limited to: events resulting in hospitalization or death, events that put patients at risk for hospitalization or death, events with significant negative consequences, worsening of psychological disorders that cause disability or that may lead to hospitalization or death, and suicidal behaviors and ideation."[99] To meet these concerns it proposed that "Midomafetamine dispensing and administration will be restricted only to certain healthcare settings certified in the REMS," and that "[a]s a condition of certification in the REMS, healthcare settings that dispense midomafetamine will be required to enroll each patient prior to treatment initiation," that "[t]he enrollment will inform patients about the risk of impairment and the serious harm that may result, the need to report adverse events, and the patient agrees to be discharged to an accompanying adult and not drive or operate heavy machinery in the immediate period after the medication session."[100] Moreover, under the FDA's vision:

> The healthcare settings are required to develop and put in place policies and procedures to ensure: (1) a prescriber is available during midomafetamine administration and monitoring and to determine if second dose is held for safety or tolerability concerns, (2) at least two healthcare providers are

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208042Orig1s000REMS.pdf [https://perma.cc/FG25-NYAU].

96. FDA, FDA BRIEFING DOCUMENT 62 (2024), https://www.fda.gov/media/178984/download [https://perma.cc/RHT9-SAYX].

97. *Id.*

98. *Id.*

99. *Id.*

100. *Id.*

> onsite, one of which must be a licensed healthcare provider, to monitor patients' medical (including vital signs) and psychological status for at least eight hours and until patient is stable to be discharged; (3) emergency action plans are in place to escalate care if needed; (4) plans are in place in case the patient requires longer monitoring; (5) the patient is stable to be discharged from the healthcare setting; (6) and that patient is released to an accompanying adult after each medication session, and (7) follow-up with patients after discharge from each medication session.[101]

Furthermore, the FDA noted that "[t]he proposed REMS also includes a patient registry to better characterize the risk of serious harm that may result from patient impairment," under which "[p]atients will be assessed during midomafetamine administration and monitoring, and after discharge from each medication session," and that "[d]ata collected through the registry may better inform us of the signs and symptoms of mental or physical distress experienced by the patient while monitored, onset and duration of short-term effects, and whether care needed to be escalated."[102] Furthermore, "information regarding patient safety between treatments will be collected including events that result in increased risk due to impaired judgement, or worsening of psychological disorders that cause disability, hospitalization, or death," and "[r]egistry data will also be used to determine whether changes to monitoring and other safe use behaviors in the REMS are needed."[103] It also recommended that "[a] REMS Assessment Plan will be developed to evaluate the proposed midomafetamine REMS," and that the "REMS design will impact the selection of metrics and data sources, which will be used to inform whether the REMS is functioning as intended and assess whether the REMS is meeting its risk mitigation goals."[104]

Because the Lykos application was not approved, we do not have a definitive decision on what a REMS for a psychedelic drug would actually be, but this submission from the agency is suggestive of its current view of the matter.[105] What is missing from the proposed REMS is any discussion of psychotherapy. Indeed, the REMS feels much more like something one would design for an inpatient surgery, with its focus on method of administration, site of administration, ensuring someone is present to take the patient home, and long-term follow-up. Perhaps surprisingly, the proposed REMS does not even mention the kind of psychosocial support or progress toward treatment goals discussed in the REMS for other drugs discussed above.[106]

Those who think that medical psychedelic use may be unsafe without such psychotherapy would view a REMS that does not require psychotherapy as a clear problem—although potentially one that could be mitigated by other non-FDA mechanisms, such as state licensure proceedings and tort law for

101. *Id.*
102. *Id.*
103. *Id.*
104. *Id.* at 61–62.
105. *See id.*
106. *See supra* Part II.A.2.

malpractice on the back end. For those who think medical psychedelic use is not unsafe per se, but that psychedelic use would be safer in the form of psychedelic-assisted therapy, the policy analysis requires understanding the "delta" as to benefits from psychotherapy versus the cost increase and its effect on access (more on that below)—the REMS statutory provision explicitly highlights a goal of "[p]roviding safe access for patients to drugs with known serious risks that would otherwise be unavailable."[107] What if one believed requiring psychotherapy would make the use of the psychedelic more effective (or effective at all)? There is an asymmetry in the way Congress wrote the statute in that REMS can be used to deal with safety concerns but not effectiveness.[108] As a result, the agency cannot impose a REMS to ensure or improve effectiveness of a psychedelic—it has to determine if it is effective without the REMS.

This Essay now discusses the implications of the REMS and label choice for business models, cost, and access.

B. Business Models

How much will be required by the approved label of the drug and the REMS is likely to be a key determinant of the business model, and indeed the likely financial success, of several firms already in or seeking to enter the business of medical use of psychedelics.

In a world (highly unlikely, I think) where there is no REMS attached to an approved psychedelic drug at all and the label permits a psychedelic to be dispensed (perhaps by specialty pharmacies) for home ingestion, then these companies can operate more like traditional pharmaceutical companies merely selling and marketing the drugs.[109]

A second possibility is a world where the REMS requires a physician (or perhaps other medical personnel) to assist with the drug administration and to monitor the patient after administration during the "trip" and for a short recovery period thereafter. The REMS might permit this monitoring to be done by nonphysician medical personnel or even nonmedical personnel with a trained physician on call at the facility. A good analogy here is to what has been required as part of the REMS for SPRAVATO®, a therapeutic formulation of ketamine used to treat depression.[110] Per the SPRAVATO® REMS, for outpatient use a healthcare setting must, among other things,

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107. 21 U.S.C. § 355-1(f).

108. *See* Amy L. McGuire, Holly Fernandez Lynch, Lewis A. Grossman & I. Glenn Cohen, *Pressing Regulatory Challenges for Psychedelic Medicine*, 380 SCIENCE 347, 348 (2023).

109. One analogy is the recent increase in flexibility that has been granted in allowing "stable" patients to take up to twenty-eight days of methadone or other opioid use disorder medications at home. *See Methadone Take-Home Flexibilities Extension Guidance*, SUBSTANCE ABUSE & MENTAL HEALTH SERVS. ADMIN., https://www.samhsa.gov/medications-substance-use-disorders/statutes-regulations-guidelines/methadone-guidance [https://perma.cc/MNH7-NJQD] (Jan. 23, 2024).

110. For more on the history of its patent and business mode, see, e.g., Mason Marks & I. Glenn Cohen, *Patents on Psychedelics: The Next Legal Battlefront of Drug Development*, HARV. L. REV. F. 212, 225–27 (2022).

"[h]ave a prescriber onsite during SPRAVATO®[] administration and monitoring"; "[h]ave healthcare provider(s) onsite to monitor patients"; certify compliance with the REMS program; "[e]stablish processes and procedures to counsel the patient on the need for enrollment [in the REMS program], monitoring, and risks of sedation and dissociation, and changes in vital signs"; ensure training for all staff on administration and counseling of patients as well as "[m]onitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours"; and maintain records and comply with audits.[111] The REMS also makes clear the drug cannot be loaned out or administered at home.[112]

A more robust set of requirements in this model for psychedelics might mirror what the FDA proposed in the Lykos MDMA provision in the REMS discussed earlier. This would include certifying healthcare settings for administration of the psychedelic and limiting its administration to those settings. It might require having a prescriber available during dose administration (including to make decisions on whether to provide a second dose on site), and "two healthcare providers . . . onsite, one of which must be a licensed healthcare provider, to monitor patients' medical (including vital signs) and psychological status for at least eight hours and until patient is stable to be discharged."[113]

A third model, the full-blown psychedelic-assisted therapy model, would involve several sessions with a psychotherapist before the drug's administration and subsequent sessions focused on integration, with the therapist also guiding the sessions.[114] For example, Professor Gründer and his coauthors envision two to eight hours of therapy before the dosing session, a dosing session where "therapists are required to remain present and available for support but explicitly refrain from active guiding or prolonged discussions," and one or two post-dosing integration sessions "intended to support participants in deriving their own insights and solutions from the experience with the psychedelic."[115]

Importantly, these three models of what the label/REMS might require give rise to different business models with different implications for cost and access. The first is essentially the business model of the typical pharmaceutical company—the company's profits turn on how much of the product it can sell. Such a strategy depends on successfully patenting and maintaining market exclusivity over a product.[116] Such a business model might coexist with a world of paraprofessionals administering or monitoring

111. FDA, CTR. FOR DRUG EVALUATION & RSCH., SPRAVATO (ESKETAMINE) RISK EVALUATION AND MITIGATION STRATEGY (REMS) 11–13 (2022), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/211243Orig1s006.pdf [https://perma.cc/CL28-4U99].

112. *Id.* at 14.

113. FDA, *supra* note 96, at 62.

114. *See* Gründer et al., *supra* note 11, at 232.

115. *Id.*; *see also* Josh Hardman, *Field Trip's Downfall: Too Early, Too Aggressive, Too Extravagant?*, PSYCHEDELIC ALPHA (March 28, 2023), https://psychedelicalpha.com/news/field-trips-downfall-too-early-too-aggressive-too-extravagant [https://perma.cc/R7Q7-RQS3].

116. For a discussion of the patent claims made in this space, see Marks & Cohen, *supra* note 110, at 225–27.

in the actual trip. One could imagine patients hiring "trip sitters" or guides with varying degrees of medical, spiritual, or just plain drug experience—but it does not seem likely that the companies selling and providing the services would "own" that part of the process.[117] As previously mentioned, it seems unlikely that the FDA will end up here.

In the second model, a pharmaceutical company continues to produce the drug and profit from sales, especially during the exclusivity period until generics enter. There is also a clinic that incurs costs associated with administration and monitoring, but it would likely profit on the facilities, personnel, any technology required, and training programs for those seeking to operate or work in such clinics. It is unclear what the relationship would be between the pharmaceutical company and the clinics. One could imagine a spectrum of possibilities, from the clinics operating independently from the pharmaceutical company, but still meeting whatever REMS certification requirements exist, to being in a licensing relationship of sorts with the pharmaceutical company, to being wholly owned subsidiaries of the pharmaceutical company. The latter may raise complications as to federal fraud statutes, including the Anti-Kickback Statute[118] and the Physician Self-Referral Law,[119] and their state equivalents, but there may be work-arounds. It may also create problems for capitalization—building an empire of clinics is capital intensive and not something that falls naturally in the bailiwick of pharmaceutical companies.

From what I can tell about how this model played out with SPRAVATO®, the clinics are not wholly owned by Janssen Pharmaceuticals but rather appear to be freestanding.[120] It is unclear whether there are any licensing or other contractual arrangements whereby the pharmaceutical company benefits beyond the sale of the drug. Oregon serves as one example of how these clinics might operate based on how the state runs its nonmedical access

117. That said, we have seen a few attempts to assert intellectual property in the form of patent claims over a method of screening candidates for psychedelic therapy and for monitoring patients during such therapy sessions. *See REMS Patents: The Next Frontier in the Psychedelics Patent Skirmish?*, PSYCHEDELIC ALPHA (Sept. 24, 2021), https://psychedelicalpha.com/news/psychedelic-bulletin-are-rems-patents-the-next-frontier-in-the-psychedelics-patent-skirmish-johns-hopkins-researcher-scores-u-s-government-grant [https://perma.cc/5XUQ-ZB3P]. An important issue, but one beyond the scope of this paper, is how REMS can be used to push away competition. The more complex the REMS regime, the higher the barrier to entry for competitors when the drug becomes generic. Although drug companies are unlikely to want a REMS, if required, they may be able to use it in this anticompetitive way. That may depend on whether some aspects of fulfilling the REMS are themselves protected under intellectual property laws and how much the FDA pushes the brand company to assist generics in participating in the brand company's preexisting REMS program.

118. 42 U.S.C. § 1320a-7b(b).

119. *Id.* § 1395nn.

120. My conclusions are based on looking up treatment centers for SPRAVATO® near me from the company's website and then quickly looking at publicly available information on those centers. I visited the following site: *Find a Treatment Center*, SPRAVATO®, https://www.spravato.com/spravato-available-treatment-centers [https://perma.cc/2KLF-86KA] (last visited April 24, 2024).

pathway, which employs licensed facilitators at licensed psilocybin service centers.[121]

In the third model, the pharmaceutical company continues to sell and make money from sales of the drug itself. The therapist providing psychedelic-assisted therapy would charge the patient for the hours of therapy just as the therapist would charge a patient coming for talk psychotherapy. Depending on the relevant rules, the therapist might be the one to administer the psychedelic, perhaps at the therapist's office or at a licensed clinic (as in the second model) depending on what is specified by the REMS.[122]

C. Cost

One way of thinking about the three models is that they progressively add on the (1) cost/regulation of the psychedelic drug itself and access to psychosocial support; (2) the site of administration, actual administration, monitoring of the patient right after administration; and (3) ongoing psychotherapy in advance, during, and after the drug administration.

Each additional step brings new business entities into the regulated market, although in some instances the same entity might play dual roles if permitted to do so (e.g., a psychotherapist providing talk therapy whose office also becomes a certified administration site for the psychedelic or a drug company and a therapy network having a common owner).[123]

Each additional step adds to the cost. I do not think one can accurately estimate the costs at the present moment: we do not know what the makers would intend to charge for their patented MDMA or psilocybin type FDA-approved, patented drugs, how their pricing strategies relate to insurance coverage, and how the branded market-exclusive prices in the

121. Marks et al., *supra* note 1, at 587. For a journalistic description of the first of the Oregon psilocybin service centers to open, see Andrew Selsky, *Oregon's New Psilocybin Service Center Invites Public to Try Psychedelic Mushrooms*, PBS (Sept. 15, 2023), https://www.pbs.org/newshour/nation/oregons-new-psilocybin-service-center-invites-public-to-try-psychedelic-mushrooms [https://perma.cc/5D2T-5BS4].

122. Again, taking inspiration from the SPRAVATO® experience, it is possible that a therapist's office could also become a certified treatment center.

123. When the same entity is playing multiple roles, there is the question of how to regulate those multiple roles. Oregon has faced a somewhat analogous problem with its nonmedical facilitator program and what happens when physicians, for example, also want to be facilitators. The current administrative rules try to force a separation between the facilitator and physician role, even if held by the same person, requiring, among other things, that "[i]f a facilitator holds a professional license in another field, the facilitator shall not exercise the privileges of that license while providing psilocybin services to clients." OR. ADMIN. R. 333-333-5130 (2024). By contrast, Colorado's draft rules for its program have "proposed two facilitator license types simply called 'Facilitator' and 'Clinical Facilitator.' Rather than separate license types, individuals holding a secondary professional license in Colorado that allows them to diagnose and treat medical or behavioral/mental health conditions may receive a Clinical Facilitator license." *Colorado's Draft Natural Medicine Rules: Full Breakdown & Commentary*, PSYCHEDELIC ALPHA (Feb. 27, 2024), https://psychedelicalpha.com/news/colorados-draft-natural-medicine-rules-full-breakdown-commentary [https://perma.cc/7VXL-JX8W].

medium-term might come down in the long-term after generic entry into the market. There is also not enough information about how many sessions and what kind of medical and nonmedical personnel might be required or offered, what variations in training might mean for rates, and the costs of operating facilities or the profit margins sought by any of the players.

That said, we can achieve a rough sense of the *relative* costs of adding each of the pieces described above together. The authors of a recent article from December 2023, aimed at estimating how costs for psychedelic-assisted therapy might come down by introducing more group rather than individual therapy at various points in a protocol, are appropriately cautious about the fuzziness of some of the estimates.[124] The authors looked at the protocols of "two psychedelic therapy trial sites: SNaP Lab's MDMA-Assisted Group Therapy for the Treatment of Veterans with PTSD (SNaP Lab); and Sunstone Therapies' Psilocybin Therapy for Cancer Patients with Major Depression (Sunstone)."[125]

The MDMA protocol involved two MDMA administrations and a longer duration, while the psilocybin protocol involved only a single administration.[126] This led the authors to use an estimate of 360 milligrams of MDMA total per patient and twenty-five milligrams of psilocybin total per patient.[127] Based on "informed estimates of the likely range of eventual prices and explor[ing] the implications of various price points in sensitivity analyses," for the drug alone, they arrived at a range of "$25 and $5 per milligram ($9,000 and $1,800) per treated patient (both MDMA sessions) for MDMA; and $1,500 and $500 per treated patient for psilocybin."[128] This figure would be a rough estimate of the cost if the drug were prescribed just like any other drug without any REMS attached.

Dr. Elliot Marseille and his colleagues' attempt to model the costs for a form of PAT, the third possibility discussed above, is more complicated because the model depends on assumptions regarding how many therapists could see how many patients, prevailing wages, and other factors.[129] Their top-line results for individual therapy estimate a total cost of $16,773 for the two-administration MDMA protocol (consisting of $710 for labs and test kits, $219 for screening and intake, and $6,804 for the clinicians, and the higher estimate of $9,000 for the MDMA itself), a number that goes down to $13,267 with a protocol that includes some group therapy by reducing the clinician time.[130] If we assume that the lab, test kits, the screening, and intake will be required even in the drug-only model, then the comparison is $9,929

124. Elliot Marseille, Christopher Stauffer, Manish Agrawal, Paul Thambi, Kimberly Roddy, Michael Mithoefer, Stefano M. Bertozzi & James G. Kahn, *Group Psychedelic Therapy: Empirical Estimates of Cost-Savings and Improved Access*, 14 FRONTIERS IN PSYCHIATRY 1 (2023).

125. *Id.* at 2.

126. *See id.*

127. *Id.* at 3.

128. *Id.*

129. *Id.*

130. *Id.* at 5.

for drug-only versus $16,773 for psychedelic-assisted therapy.[131] In other words, 41 percent of the cost of that higher number is the therapy elements (the number is $13,627 with group therapy elements).[132] For the psilocybin protocol—again taking the higher drug cost of $1,500, lab costs of $632, and screening/intake costs of $219, and assuming that the lab and test kits and the screening and intake will be required even in the drug-only model—they estimate an additional $2,827 for the clinician time for individual therapy (55 percent of the total cost) for a total of $5,178.[133] Using group therapy instead, the clinician time amounts to $1,846 (44 percent of the total cost) for a total cost of $4,197.[134]

The chart below summarizes the costs by assuming the (higher) individual therapy only model:

	Drug Only	Drug & Individual Psychotherapy
MDMA (two administrations)	$9,929	$16,773
Psilocybin (one administration)	$2,351	$5,178

What about the potential middle-ground approach requiring physician involvement in administration, monitoring, and available social support? This cost is hard to estimate because it may depend on how many individuals must be present during the drug administration session and what the individuals' educational qualifications have to be. The total cost may also depend on the cost of maintaining a facility if the certification requirements make doing it in a typical doctor's office infeasible. But I think a very rough guess is that the cost will fall between the two estimates above. Some clinician time will be required, but it will be substantially less (maybe one third less but that is a very rough guess) than what is provided in the psychedelic-assisted psychotherapy model. On the other side of the ledger, maintaining the infrastructure for psychosocial support without psychotherapy might add some costs. Finally, there is the question of how each additional player may seek profit margins and whether that will alter these very rough assessments.[135]

131. *Id.*
132. *Id.*
133. *Id.*
134. *See id.* tbl.1.
135. A different way to try to estimate the cost would be to look at comparable options already operating. The Oregon psilocybin service centers, involving a nonmedical pathway using facilitators, might offer one such estimate. A "client can wind up paying over $2,000, which helps cover service center expenses, a facilitator and lab-tested psilocybin. *See* Selsky, *supra* note 121. Ketamine provides a different analogy. In The Washington Post, Rachel Zimmerman reports:

> Six ketamine infusions over two to three weeks at a psychiatrist's office, including an in-depth, pretreatment consultation and post-treatment follow-up, can run up to

A different attempt to estimate cost—this time only for MDMA-assisted therapy for PTSD—was published in a draft report by the Institute for Clinical and Economic Review (ICER) on March 26, 2024, suggesting a price for MDMA of approximately $5,000 to $15,000 per course (for all three sessions), and nondrug costs of $13,118 for all sessions in total.[136] These nondrug costs include pregnancy tests for women ($85), psychological testing and evaluation ($241), psychiatric diagnosis interview examination with two therapists ($438), ninety-minute preparation sessions ($1,324), an eight-hour MDMA session with two therapists ($7,059), and a ninety-minute integration session ($3,971).[137]

D. Access

Access to a medicalized psychedelic pathway is directly related to these cost differentials. From the simple prescription drug model, to a model of administration and monitoring at a certified facility and some psychosocial support, to more expansive psychedelic-assisted therapy, the costs and barriers to access increase. For policymakers, the question is whether the cost increase and access diminution are worthwhile for increases in safety and efficacy of the intervention.[138] All stakeholders would likely agree that we do not yet have strong empirical evidence to help us break out just how much improvements in safety and efficacy add in costs.

However, there is a more complicated relationship between the layers and access since some patients are partially or completely insulated from some of the cost differences by public or private health insurances. To determine the effects of insurance, we need to disaggregate reimbursement for the drug itself, the cost of administration and monitoring individuals while on a trip, and the costs of psychotherapy in a psychedelic-assisted therapy design.

Here, there has been some recent good news for those hoping that some elements will be covered. As one report explains, "[m]edical codes provide healthcare organizations—including providers, systems, and payers—a uniform way to accurately describe and efficiently categorize medical items,

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> $4,500. At-home ketamine businesses typically offer the therapy at a lower price point: Mindbloom, for instance, charges $1,158 for a six-session treatment plan with virtual support; it is $768 for six follow-ups. While some people achieve remission after one round of treatment, some others require monthly boosters.

Rachel Zimmerman, *Is Ketamine Therapy Safe?: Answers to Questions After Matthew Perry's Death*, WASH. POST (Dec. 16, 2023), https://www.washingtonpost.com/wellness/2022/09/12/ketamine-therapy-explained/ [https://perma.cc/X8V5-7YVN].

136. REEM A. MUSTAFA, BRETT MCQUEEN, DMITRIY NIKITIN, EMILY NHAN, ANTAL ZEMPLENYI, MICHAEL J. DISTEFANO, YASMINE KAYALI, MARINA RICHARDSON & DAVID RIND, INST. FOR CLINICAL & ECON. REV., 3,4-METHYLENEDIOXYMETHAMPHETAMINE ASSISTED PSYCHOTHERAPY FOR POST-TRAUMATIC STRESS DISORDER (PTSD) 28 (2024), https://icer.org/wp-content/uploads/2024/03/PTSD_Draft-Report_For-Publication_03262024.pdf [https://perma.cc/2GK5-L88U].

137. *Id.*

138. This is very much the debate that I discuss above. *See supra* Part I.

services, and procedures."[139] Among these codes are Current Procedural Terminology (CPT) codes, developed by a panel convened by the American Medical Association, which are national codes for reimbursement for physicians and other health care professionals' services.[140] In June 2023, with an effective date of January 1, 2024, the AMA promulgated new Category III CPT codes that:

> describe the provision of one hour of continuous in-person monitoring and intervention (including psychotherapy or crisis intervention) during what the AMA refers to as "psychedelic medication therapy." The codes may be used by a physician or other qualified healthcare professional (QHP) (0820T), a second physician or QHP, concurrently with the first physician or QHP (0821T), and clinical staff under the direction of a physician or other QHP (0822T).[141]

That said, the fact that it is a Category III code carries some limitations:

> First, Category III codes are temporary; they are archived five years after publication, though use may be extended or they may be converted into Category I codes. Second, Category III codes are not considered by the AMA's Relative Value Scale Update Committee (RUC), which provides CMS with recommendations on the Relative Value Units (RVUs) assigned to each code. RVUs are used by Medicare and other third-party payers to calculate payment rates for each code; without an RVU, a code does not have a standardized payment. Finally, because Category III codes are assigned to emerging technologies, services, and procedures, public and private health insurers often consider them experimental, investigational, and unproven, and only cover and reimburse such codes on a case-by-case basis.[142]

Moreover, the CPT codes for the preparatory and integration sessions are lacking now. As BrainFutures argues in its report:

> There is currently no code, or set of codes, for a 90-minute psychotherapy session, which is the duration of preparatory and integration psychotherapy in several clinical trials. This leaves many mental health providers without any method to bill for the 90-minute or longer sessions considered by experts in the field to be prerequisite to the delivery of effective psychedelic-assisted therapy . . . . Codes to extend psychotherapy beyond 60 minutes were eliminated effective January 1, 2023. A replacement code for use by all clinicians eligible to bill for psychotherapy is reportedly in development, signified by a placeholder code. However, at this time, only clinicians eligible to use evaluation and management codes (i.e. physicians, nurse practitioners, etc.) are able to bill for longer sessions.[143]

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139. BRAINFUTURES, A GUIDE TO CPT AND HCPCS CODES FOR PSYCHEDELIC-ASSISTED THERAPY 6 (2023), https://www.brainfutures.org/wp-content/uploads/2023/09/A-Guide-to-CPT-and-HCPCS-Codes-for-Psychedelic-Assisted-Therapy.pdf [https://perma.cc/A2BH-P4GY].

140. *Id.*

141. *Id.* at 7.

142. *Id.*

143. *Id.*

Much of the report is devoted to giving practitioners suggestions on how to use other preexisting coding options for "preparation, integration, and the medication administration session, reflecting the coding challenges presented by the duration of the session and participation of multiple providers."[144] It also suggests much will come down to negotiation between payers and providers.[145]

Experience with insurance coverage for ketamine also suggests several cautions.[146] For example, insurers may be reluctant to pay for prescriptions for "off-label" uses, that is those outside of the specific uses for which FDA approval is achieved and reflected on the drug label.[147] That said, the drug-psychotherapy combination involved in the model is unusual. One could see insurers agreeing to pay for the drug and administration and monitoring sessions and perhaps a single preparatory session, but not for multiple pre-administration true psychotherapy sessions or true psychotherapeutic integration sessions on the back end. Insurers' willingness to pay for these additional elements will likely depend on providers of these additional elements showing improvements in safety and, in particular, efficacy, when these elements are included. It will be important to convince insurers that these sessions produce significant improvements in PTSD, major depressive disorder, or whatever the FDA-approved use is, and that these improvements will help insurers reduce costs they would otherwise incur as to patients with such diagnoses. The nature of the label the FDA approves and what the REMS does or does not say about psychotherapy as opposed to psychosocial support may create something of a baseline against which insurance negotiations take place. There may also be the opportunity for third-party psychedelic-specific insurance products to enter the market as add-ons. We have seen some fledgling attempts in the ketamine context.[148]

One possible future is a market with several different access points: cheaper options focused primarily on the drug; monitored administration and monitoring during the trip and some wraparound available psychosocial support, most of which will be covered by insurance; and more expensive psychedelic-assisted therapy options with multiple psychotherapeutic preparation and integration sessions, much of which will not be covered by insurance. Such a world would mirror current treatment realities for depression, for example, wherein many more people can get insurance-covered prescriptions of selective serotonin reuptake inhibitors than can get insurance-covered ongoing talk psychotherapy. But that reality

144. *Id.* at 12.

145. *Id.*

146. *See* Vincent Joralemon, *Insurance Coverage for Psychedelic Therapy*, BILL OF HEALTH (Mar. 24, 2024), https://blog.petrieflom.law.harvard.edu/2024/03/27/insurance-coverage-for-psychedelic-therapy/ [https://perma.cc/3WD3-7BQ7].

147. Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377, 392 (2014).

148. *See id.*

is disappointing for those who view the primary role of psychedelics as enabling psychotherapy to do its work.[149]

Such variation is all for the better, one might say. But these pathways may be in competition with one another. Will patients pay out of pocket for the psychedelic-assisted therapy when they can get the prescription-plus-psychosocial support completely covered? What is more, there remain open questions about how the multiple tracks of medicalized models and their costs and pricing will "compete" with nonmedicalized facilitator models like the one in Oregon. It is true that we have thus far seen multiple branching paths of policy reform—supported adult use of the kind in Oregon, decriminalization approaches in some localities and states, and a potential FDA-approval path. However, once people come to view MDMA or psilocybin as an FDA-approved drug they might like to try for a medical or nonmedical reason. How will they choose among the multiple pathways of access? Perhaps more pertinently, will we see policy competition post-FDA approval that may edge out everything but the FDA-approved pathway?[150]

The recent failure of Lykos's FDA process is no doubt dispiriting to many who believe that psychedelics have much to offer the world of medicine.[151] But it has highlighted the key question with which this Essay has wrestled: Will the future of medical psychedelics see them serving as a drug or more as a technology assisting psychotherapy? There is much work to do on determining the safety and effectiveness of various points along this continuum, but this Essay has shown that the answer to the key question will also have profound impacts on business models, costs, and access. Moreover, this Essay has endeavored to show how this decision may be guided as much by how the FDA sees its regulatory role and the limits on its REMS authority as it is guided by the underlying medicine.

149. *See supra* Part I.

150. For some early thoughts by me, see I. Glenn Cohen, *Branching Regulatory Paths and Dead Ends in Psychedelics*, REGUL. REV. (Apr. 15, 2024), https://www.theregreview.org/2024/04/15/cohen-branching-regulatory-paths-and-dead-ends-in-psychedelics/ [https://perma.cc/PJG9-76MJ].

151. *See supra* notes 4–5 and accompanying text.