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RESEARCH REPORT

An estimate of the number of people with clinical depression eligible for psilocybin-assisted therapy in the United States

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This study aims to estimate the lower, middle, and upper bounds of potential demand for psilocybin-assisted therapy (PSIL-AT) for major depressive disorder (MDD) and treatment-resistant depression (TRD) in the United States. We calculated potential PSIL-AT demand for MDD and TRD by estimating the number of U.S. patients with MDD, identifying those in treatment, and determining who qualifies as having TRD. We established a range of estimates using the exclusion criteria from the largest trials to date on PSIL-AT for MDD or TRD. Estimates ranged from lower-bound through stringent criteria, mid-range by focusing on likely real-world scenarios, to upper-bound by accounting for double counting for patients with multiple comorbidities. A significant portion of patients with MDD and TRD is ineligible for PSIL-AT due to disqualifying conditions. Percentage of patients who are eligible are 24% (lower-bound), 56% (mid-range), and 62% (upper-bound). Variance was largely influenced by the removal of alcohol and substance use disorders as exclusion criteria, as well as removing the double counting from comorbid psychiatric and cardiovascular conditions. The analysis outlines the public health implications of providing PSIL-AT for MDD and TRD, emphasizing that the effective demand will be shaped by insurance coverage, state-level regulations, and the availability of trained providers. These findings suggest the need for careful policy planning and resource allocation to ensure equitable access and effective implementation of PSIL-AT across diverse populations and regions.

Keywords: Psilocybin, depression, exclusion criteria, psychedelic therapy.

Introduction

Psilocybin-assisted therapy (PSIL-AT) has been designated by the Food and Drug Administration (FDA) as breakthrough therapy for patients with either a diagnosis of major depressive disorder (MDD) or treatment-resistant depression (TRD) (1). TRD is defined as having at least two treatments with antidepressant medications, at adequate doses and for an adequate duration in the current depressive episode, without significant relief from symptoms related to MDD (2). Recent clinical trials have defined inclusion and exclusion criteria specifically for TRD (3) or MDD (4, 5), the latter of which may also include patients with TRD. As FDA approval and subsequent legalization for medical use of psilocybin is now being considered (6), it is important to understand the possible public health impact from the introduction of PSIL-AT in the United States. This, in turn, requires an estimation of the potential demand. We chose to define a clinical lower-bound, mid-range, and upper-bound estimates of the demand for PSIL-AT as a treatment for MDD or TRD.

Results

As shown in Table 1, of the 14.8 million people with MDD, 9 million are being treated, and 2.7 million meet criteria for TRD.

Table 2 illustrates the percentage of patients deemed eligible for PSIL-AT, accompanied by corresponding estimates for the number of individuals being treated for MDD or TRD who are eligible for this therapeutic approach.

The lower-bound estimate indicates only 24% of patients with depression would meet strict clinical trial exclusion criteria for PSIL-AT. This amounts to 2.2 million patients currently undergoing treatment for MDD or 0.6 million patients when considering only those with TRD.

In applying exclusion criteria likely to operate in real-world clinical settings (the mid-range estimate), we observe a notable increase in the proportion of included patients to 56%. Application of these more permissive criteria would expand the pool of eligible patients being treated for MDD or TRD to 5.1 million or 1.5 million, respectively. The exclusion of alcohol and substance use disorders accounts for a significant portion of this adjustment, contributing to 32% of the difference.

Finally, the upper-bound estimate, which adjusts for double counting between different medical conditions, raises the estimate to 62% of the patient population with depression being eligible for PSIL-AT. This translates to 5.6 million individuals and 1.7 million eligible for PSIL-AT when considering MDD and TRD, respectively. This adjusted increase is primarily attributed to the co-occurrence of cardiovascular and psychiatric comorbidities, with each contributing to a 3%–4% increase in eligible patients.

In addition to our base estimates, we conducted a sensitivity analysis to evaluate the impact of varying assumptions on the overall demand projections for PSIL-AT. Specifically, we assigned beta distributions with a range of plus or minus 50% of the baseline values to each of the comorbidity prevalence estimates shown in column 3 of Table 2. Using @RISK (Palisade Corporation, version 8.1.1) software, we simulated the overall uncertainty in the final estimates of the number of patients eligible for PSIL-AT among those with MDD and TRD.

The results of the sensitivity analysis are depicted in Figures 1 and 2. For patients with MDD, the analysis produced a 95% confidence interval (CI) of 4.7 million to 6.6 million eligible individuals, while for patients with TRD, the 95% CI ranged from 1.4 million to 1.9 million. These ranges highlight the potential variability in our estimates based on changes in the assumptions underlying comorbidity prevalence, emphasizing both the robustness and the uncertainty inherent in our projections.

Discussion

This analysis outlines the dimensions of the public health implications of providing PSIL-AT for the treatment of MDD and TRD. Our estimates of

Table 1. Estimates of number of people who would qualify as having MDD, those in treatment, and those who have TRD

Population	% of MDD population	Number of patients	Source
Patients with MDD in United States	–	14,800,000	(7)
Patients with MDD who received treatment in past year	61%	9,028,000	(2)
Patients with MDD who experience 2+ treatment failures (TRD)	30%	2,708,400	(2)

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Table 2. Prevalence of disqualifying comorbidities in the largest clinical trials utilizing PSIL-AT for MDD or TRD with number of patients eligible

Disqualifying comorbidities	Trials with this exclusion criterion	Prevalence of disqualifying comorbidity in patients with MDD or TRD according to: 1. Trial exclusion criteria[1] CI (Confidence Interval), OR (Odds Ratio), SE (Standard Error)	2. Real-world exclusion criteria	3. Real-world exclusion criteria adjusted for comorbid conditions[2,3]
Psychotic or manic disorder	(3–5)	19% (8)	19% (8)	23.2% (9)
Suicide attempt in the past year		8.0% [95% CI=(3–14%)] (10)	8.0% (10)	
Diabetes, uncontrolled	(5)	2.9% [OR=1.4 (1.4–1.5)] (11, 12)	2.9% (11, 12)	8.0% (13, 14)
Stroke	(3–5)	1.9% [OR=2.4 (2.0–2.8)] (11)	1.9% (11)	
Heart attack in last year	(3–5)	2.7% [OR=0.9 (0.8–1.1)] (11)	2.7% (11)	
BP 140+/90+, treatment-resistant		2.0% [OR=1.4 (1.3–1.4)] (11, 15)	2.0% (11, 15)	
Epilepsy		3.7% [OR=2.6 (2.3–3.0)] (11)	3.7% (11)	3.7% (16)
Personality disorder	(4)	2.2% [SE=.36] (16)	2.2% (17)	2.2% (11)
Hepatic impairment (Child-Pugh > 7)[4]	(5)	1.8% [SE=.10] (18)	1.8% (18)	1% (17)
Alcohol dependence	(3–5)	20.0% (19)	–	
Drug dependence		12.0% (19)	–	–
Other cardiac conditions (Long QT, cardiac hypertrophy, heart failure, tachycardia at rest, atrial fibrillation, prosthetic valve)	(5)	–	–	–
Pregnancy		–	–	–
Unwillingness to discontinue SSRIs		–	–	–
Unwilling or unable to discontinue formal psychotherapy		–	–	–
Have used psychedelics in the past 5 years; have used psychedelics 10+ times in the past		–	–	–
Have 1st degree relative with psychotic disorder or bipolar disorder		–	–	–
Received ECT or TMS in the past 90 days	(5)	–	–	–
Percentage of patients who would be ineligible for PSIL-AT	–	76%	44%	38%
Percentage and number of patients with MDD and TRD eligible for PSIL-AT				
Percentage of patients eligible for PSIL-AT	–	24%	56%	62%
Number of patients being treated for MDD who are eligible for PSIL-AT	–	2.2M	5.1M	5.6M
Number of patients being treated for TRD who are eligible for PSIL-AT	–	0.6M	1.5M	1.7M

[1] Where available, confidence intervals, odds ratios, and standard errors were reported.
[2] Double-counting calculations used prevalence estimates from the general population and are not MDD-specific.
[3] For sensitivity analysis, each comorbidity was assigned a beta distribution with alpha and beta parameters of 2 and maximum/minimum values of +/−50%
[4] Hepatic impairment estimates came from the general population and are not MDD-specific.

demand are subject to contingencies pending FDA decision around PSIL-AT. One possibility that could elevate demand beyond our projections involves off-label use of PSIL-AT for conditions other than depression. Evidence from psychiatric prescription practices suggests that psychiatric medications are used to treat a range of conditions outside their original FDA-approved indication. A retrospective analysis, for example, revealed that 91% of patients currently prescribed antidepressants would not meet randomized clinical trials eligibility based on their medical status (20). This discrepancy suggests that the eligibility for PSIL-AT might be significantly higher than our estimates if PSIL-AT is used to treat other medical conditions such as anxiety disorders, chronic pain, and other psychiatric disorders, either off-label or following eventual FDA approval for these conditions. We are aware of no reliable data that would allow us to estimate current and especially future prevalence of treatment seeking, which introduces further complexity into our demand projections.

Conversely, other psychedelics granted FDA breakthrough status such as lysergic acid diethylamide for general anxiety disorder (21) may be used off-label in the future to treat patients with MDD or TRD given high comorbidity between these conditions (22). If these other psychedelics are given FDA approval in the future, the demand estimate would need to be modified to distribute across the relative uptake of all psychedelics that have therapeutic effects on depression.

Additionally, there are countervailing practical considerations for PSIL-AT which are likely to constrain effective demand to levels lower than our estimates. These include the availability of trained providers, geographical access to therapy, and patient preferences related to cost, treatment duration, and cultural acceptability. For example, patients living in urban centers are likely to have greater access to PSIL-AT facilities and therapists, while rural areas may lack sufficient trained professionals and infrastructure for effective administration. States that have already legalized psychedelic therapies like Oregon and Colorado may asymmetrically dominate demand in the short-term while other states work through establishing their own regulatory framework for PSIL-AT.

Recent clinical trials have evaluated psilocybin's effectiveness as both monotherapy for depression (3, 4), and as an adjunct to established

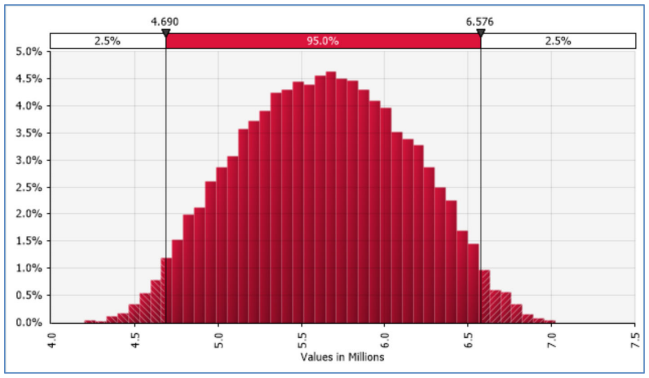

Figure 1. Patients being treated for MDD who are eligible for PSIL-AT. Multivariate sensitivity analyses, 20,0000 iterations.

antidepressant regimens (2, 23). In a 2020 article, Luo *et al.* reported that 70% of individuals with MDD utilize antidepressants (24). Therefore, if FDA approval of PSIL-AT for MDD restricts it to monotherapy, its applicability would be significantly narrowed, given evidence suggesting that nearly half of patients attempting to taper off psychotropic drugs face difficulties in completely stopping their medication (25).

Heterogeneity in the ways states choose to implement PSIL-AT will also impact effective demand. Existing legalization efforts in Colorado and Oregon may serve as a model for how PSIL-AT is rolled out nationwide post-FDA approval. Colorado's Natural Medicine Health Act, for example, mandates that licensed facilitators refrain from treating patients with many of the comorbidities discussed in this paper (26). However, patients may get clearance from a medical professional to proceed with psychedelic therapy despite exclusionary conditions (26). Whether states choose to follow Colorado or Oregon's example or implement their own regulations is unknown and makes demand estimation difficult.

Perhaps most importantly, the prospective demand will be shaped by the extent to which insurers, both public and private, include PSIL-AT in their coverage schemes. Medicaid is the largest health care payer in the United States. It covered 85 million low-income beneficiaries in 2023 (27) and 18%–20% of its beneficiaries are likely to have clinical depression (28). Thus, decisions Medicaid makes regarding the conditions under which PSIL-AT services are made available and reimbursed will be particularly important in determining effective demand. Ultimately, whether PSIL-AT has a significant impact on the mental health of the U.S. population depends on the decisions of public and private third-party payers, and Medicaid is the single most important among them.

The range of eligibility estimates (24%–62%) highlights the need for flexible healthcare planning and resource allocation strategies. Policymakers and healthcare providers must prepare for this variability by ensuring that sufficient resources—including trained therapists, facilities,

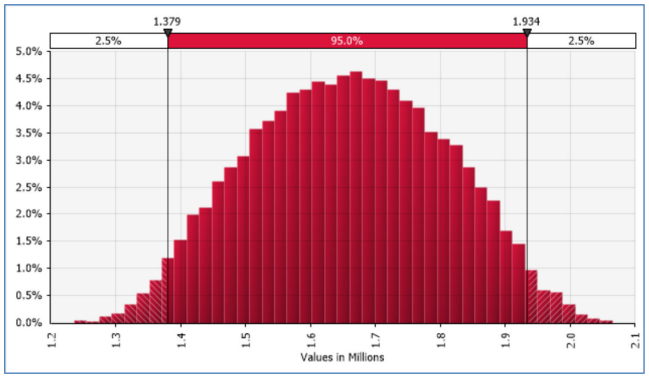

Figure 2. Patients being treated for TRD who are eligible for PSIL-AT. Multivariate sensitivity analyses, 20,0000 iterations.

and financial support—are available to meet demand under various scenarios. This flexibility will be crucial as more data becomes available post-FDA approval, allowing for adjustments in resource distribution and ensuring equitable access to PSIL-AT across diverse populations and regions.

This study serves as a basis for policymakers, healthcare payers, and pharmaceutical companies to gauge the potential public health impact of PSIL-AT pending FDA approval. As the field progresses, further research is warranted to explore psilocybin's therapeutic range, including its application to a broader array of mental health conditions and its integration into nonclinical settings. Future studies should focus on regional and demographic variations, the role of state regulations, and cultural attitudes toward psychedelic therapies. Additionally, longitudinal studies tracking the real-world implementation of PSIL-AT will be essential for assessing how initial projections align with actual demand, influencing future policy decisions and resource allocation efforts. Such analyses will refine our understanding of the potential public health impact of psychedelic therapies and help to guide policy and clinical practice.

Methods

Overview

To calculate the potential demand for PSIL-AT for TRD and MDD in the United States, we estimated the number of patients with MDD, identified how many of these patients are currently undergoing treatment, and further defined who would qualify as having TRD. We established a range of estimates: a lower-bound estimate through stringent application of exclusion criteria used in clinical trials; a mid-range estimate by considering only exclusion criteria likely to be relevant to real-world clinical scenarios; and an upper-bound estimate by refining our analysis to account for patients with two or more comorbid conditions in addition to MDD. Since each comorbidity would exclude potential patients from safely accessing PSIL-AT, we eliminate the double counting that would result from co-occurring disqualifying conditions.

We used an estimate of MDD cases in the United States based on the 2021 National Survey on Drug Use and Health (6). We then focused on the subgroup of individuals who had received treatment for their MDD in the past year and further adjusted to estimate the number of individuals who would qualify as having TRD (1).

In focusing on individuals currently undergoing treatment for depression, our approach ensures that demand estimates are grounded in real-world clinical settings, where PSIL-AT will likely be administered should they receive FDA approval. This allows us to work with a population whose treatment-seeking behaviors and clinical profiles are well documented, providing a reliable foundation for demand estimation. By choosing this baseline, we also avoid speculative assumptions about the future behavior of untreated individuals (acknowledging a potential influx post-FDA approval), ensuring that our projections remain conservative and methodologically consistent. Moreover, this approach allows for flexibility, as future research and data collection can expand upon these estimates by incorporating the potential uptake of PSIL-AT among currently untreated individuals.

A portion of this patient population fails to meet clinical eligibility for PSIL-AT due to a disqualifying medical condition. To estimate the portion of such disqualified patients, we identified the clinical exclusion criteria from the largest clinical trials to date on PSIL-AT for MDD or TRD (3–5) (see Additional Materials). Where available, we included confidence intervals and error margins from prevalence data looking at depression with different comorbidities. We constructed three different estimates of the potential demand for PSIL-AT based on three respective sets of assumptions regarding eligibility for PSIL-AT:

1. All patients with the exclusion criteria used in clinical trials, assuming no comorbid medical conditions. This represents the theoretical lower-bound of patients who would be eligible for PSIL-AT and is represented as the column labeled "1. Trial exclusion criteria" in Table 2.
2. Same as #1 but removing exclusion criteria that would be relevant in a clinical trial setting but would not apply in real-world clinical settings. This represents a mid-range estimate and is labeled "2. Real-world exclusion criteria" in Table 2.

3. Same as #2 but with further adjustment for the prevalence of comorbid medical conditions (e.g., psychosis and acute suicide risk). This represents an upper-bound estimate and is represented as "3. Real-world exclusion criteria adjusted for comorbid conditions" in Table 2.

We applied these sets of assumptions twice, to patients with MDD and to patients with TRD.

Across all estimates, we did not gather prevalence data on medical conditions that were transient (i.e., pregnancy), modifiable with a provider (i.e., tapering of a SSRI), niche with little to no reliable prevalence data available in patients with depression (i.e., diagnosed psychosis in first-degree family members or cardiac arrythmias), constructs of effective study design (i.e., discontinue existing psychotherapy or previous psychedelic use), or experimental (i.e., deep brain stimulation or vagal nerve stimulation).

In evaluating "2. Real-world exclusion criteria", we considered both the pharmacological mechanisms of psychedelic agents and the clinical insights of one of the paper's authors (Raison). Our premise is that the neurobiological effects of psilocybin will be the same in real-world clinical practice as they are in trials, thus warranting our inclusion of conditions known to be affected directly by these neurobiological mechanisms in our demand estimation. The neurological mechanism of psilocybin (29) is thought to destabilize underlying mania and psychosis (30), trigger latent epilepsy (31), and exacerbate acute suicide risk (32). PSIL-AT also exhibits underlying serotonergic effects on the body (33), which are known to cause cardiovascular stress exacerbating risk of stroke, heart attack, diabetic complication, and other sequela of hypertension (34). Additionally, severe liver dysfunction may alter the metabolism of psychotropic medications, necessitating its inclusion as a criterion for exclusion in clinical practice (35).

The benefits of PSIL-AT for the treatment of personality disorders have been discussed but are currently unsubstantiated (35) and we therefore retain it as an exclusion criteria in this analysis. We removed alcohol use disorder and substance abuse disorder from our list of exclusion criteria because evidence suggests that PSIL-AT can be beneficial for patients with these conditions (31, 36).

To avoid double counting, we then refined the resulting estimate based on the prevalence of comorbidity between the different exclusionary conditions. This is represented as "3. Real-world exclusion criteria adjusted for comorbid conditions" in Table 2. When available, we used the prevalence of comorbid conditions among people with clinical depression. Where this was not possible, we used estimates of the prevalence of comorbid conditions in the general population. For example, the 12-month incidence of suicide attempts among patients reporting psychosis and any other psychiatric condition, in this case clinical depression, was 47.4% (9). Utilizing these data, we adjusted for the potential double counting of patients ineligible due to both psychosis and acute suicide risk, resulting in a revised combined prevalence of 23.2%. Similarly, we found high comorbidity between uncontrolled diabetes (13), stroke, heart attack, and treatment-resistant hypertension (14) and formulated a total estimate of 8.0%.

Author Contributions

SFR: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Project administration.
CLR: Writing – Review & Editing, Supervision.
EM: Writing – Review & Editing, Supervision.
All authors discussed the results and contributed to the final manuscript.

Designation of Corresponding Author and Lead Contact

SFR is designated as the corresponding author and lead contact for this paper. He has taken responsibility for coordinating the effort, overseeing the data integrity, handling the submission process, and communicating with the journal pre- and post-publication. SFR ensures that all authors have approved the final version of the manuscript and adhere to all editorial and submission policies.

Conflicts of Interest

SFR confirms that he was a consultant at Sunstone Therapies. EM serves as adjunct faculty at UC Berkeley's Collaborative for the Economics of Psychedelics which has received financial support from the Usona Institute. CLR discloses that he serves as a consultant for Usona Institute, Otsuka, and Novartis. There are no other conflicts of interest among the authors, and all authors have disclosed any related work under consideration elsewhere.

All authors have agreed to the order of authorship, affirming their contributions to the work as detailed above. In case of any authorship disputes, the authors will resolve them internally without involving the journal editorial process.

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