Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Psilocybin Review***
-August 2024-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) conducted a therapeutic review of psilocybin use in certain mental health conditions. This is the first review of psilocybin by the NPTC. The committee ultimately made **no modifications** to the National Core Formulary following this review.

After Albert Hoffman, a scientist who also discovered lysergic acid diethylamide (LSD), isolated psilocybin from *Psilocybe mexicana* in 1957 and then chemically synthesized it in 1958, psilocybin has been a subject of research, but research in the U.S. ended in 1970 with the passage of the Controlled Substance Act.[1,2,3,15] As of 2018 and 2019, the U.S. Food and Drug Administration has granted breakthrough therapy status to psilocybin for Treatment-Resistant Depression (TRD) and Major Depressive Disorder (MDD), respectively.[1,2] Two states, Oregon and Colorado, have moved towards the provisioning of psilocybin in established centers.[3] Oregon is the first and only state with a Therapeutic Psilocybin Program complete with an Advisory Board, which instructs the Oregon Health Authority to license and regulate psilocybin.[3] There are no clinical guidelines informing the therapeutic use of psilocybin. However, New Zealand and Australia have authorized psychiatrists to prescribe psilocybin for TRD.[4] In Canada, access is limited to clinical trials, a special access program, or at the discretion of the Ministry of Health.[5]

Psilocybin is part of an investigational treatment modality called “Psilocybin Assisted Therapy” which shows potential utility for mental health, particularly in MDD and TRD with or without cancer.[6] Ongoing research is also occurring for other potential indications including Post Traumatic Stress Disorder (PTSD), Alcohol Use Disorder, and Tobacco Use Disorder.

Discussion:

Psilocybin is classified as a “classic serotonergic psychedelic drug” along with N,N-dimethyltryptamine (DMT), mescaline, and LSD which has been known to cause subjective, perceptual, dissociative distortions of space-time and ego dissolution.[7,8] It is a prodrug found in over 200 species of mushrooms (genus: *psilocybe*) that when consumed orally, is rapidly dephosphorylated in the stomach to its psychoactive moiety, psilocin. Its onset of action is 10-40 minutes post ingestion on an empty stomach and has a duration of approximately 2-6 hours (or longer) depending on the dose.[8,9] Psilocin’s chemical structure is similar to serotonin.[1,2,7] Eighty percent of psilocybin is metabolized by the liver, and a portion is excreted as free psilocin in the urine within 24 hours post-ingestion.[8,9,15] Psilocin exerts its effects primarily as an agonist at the 5-HT_{2A} receptor which plays a key role in regulating mood and anxiety.[7,8,9]

Though psilocybin’s mechanism of action is not fully clear, theories focus on parts of the brain collectively known as the Default Mode Network (DMN). The DMN, comprised of the medial prefrontal cortex (mPFC), posterior cingulate cortex, and the angular gyrus and their associated interconnected brain regions are densely populated by 5-HT_{2A} receptors.[10] The mPFC and the hippocampus (HC) are two brain regions affected by depression. Additionally, the brain regions of the mPFC and HC appear to be elevated in people with MDD. One theory known as the “relaxed beliefs under psychedelic and the anarchic brain” hypothesize psilocybin’s ability to reset the wiring governing the brain’s default information processing by blocking neural activity through the DMN, forcing the brain to create new neuronal connections thereby opening a therapeutic window to facilitate the emergence of novel insights, potentially leading to emotional release.

Scientifically validated risk assessment tools for identifying individuals with increased likelihood of benefit or harm from psilocybin-assisted therapy do not currently exist.[11] Risk assessment should include physical and mental health considerations.[11] Although clinical trials have excluded those with a history of psychotic disorders, in Oregon, contraindications to psilocybin use include a prescription for lithium in the last 30 days, thoughts of causing or wanting to cause harm to self and others, as well as a diagnosis of active psychosis or treatment for active psychosis.[12] Additionally drug interactions with antidepressants, antipsychotics, and mood stabilizers have not been studied, therefore risk for serotonin syndrome or serotonin toxicity remains unknown.[16] Psilocybin can potentially increase blood pressure and cause tachyarrhythmias in those with uncontrolled blood pressure, heart disease or arrhythmias; it has been shown to increase QTC interval by a mean of 2.1 milliseconds.[11,13]

In a meta-analysis of 6 randomized, double-blind clinical trials (RCTs) assessing acute psilocybin adverse effects (AE), psilocybin was associated with greater AEs of the following within 24 hours of administration: headache (RR, 1.99; 95% CI: 1.06-3.74; p=0.04), nausea (RR, 8.85; 95% CI: 5.68-13.79; p<0.001), anxiety (RR, 2.27; 95% CI: 1.11-4.64; p=0.02), dizziness (RR, 5.81; 95% CI: 1.02-33.03; p=0.047), and elevated blood pressure (RR, 2.29; 95% CI: 1.15-4.53; p=0.02) compared with control.[14] Psilocybin was not associated with risk of paranoia and transient thought disorder.[14]

Though existing short-term clinical trials have not documented cases of potential long-term risk and safety concerns, this needs further study. The development of a hallucinogenic use disorder or hallucinogen-persisting perception disorder is theoretical as it appears there is low risk of developing physical or psychological dependence with prescribed clinical use.[16] However, it cannot be ruled out as it may be a concern to those who need multiple psilocybin doses in order to maintain therapeutic effects.[16] Psilocybin tolerance may occur with repeated use, but development of physical dependence does not appear to occur.[9,15]

Currently there is more data regarding psilocybin effects on depression with or without cancer. In an evidence review by the Veterans Affairs[17] and the Oregon Psilocybin Advisory Board[11], two small RCTs[18,19] evaluated psilocybin for the treatment of depression. In a randomized crossover trial of two psilocybin doses (20mg/70kg and 30mg/70kg, 1.6 weeks apart) with a wait-list control, participants with moderate-to-severe depression (n=24) displayed reductions in GRID-Hamilton Depression (GRID-HAMD) rating scales that favored psilocybin, showing a large effect size at week 5 (Cohen's d=2.5, p<0.001) and week 8 (d=2.6, p<0.001).[18] At 12 months, 75% of participants experienced a clinically significant response, defined as a ≥50% decrease from their pre-treatment GRID-HAMD score, and 58% met criteria for disease remission, defined as a GRID-HAMD total score of 7 or lower.[18] In a RCT of two psilocybin doses of 25mg vs. escitalopram 10-20mg/day for 6 weeks for treatment of MDD (n=59), participants in both arms showed decreases in Quick Inventory of Depressive Symptomology-Self-Report (QIDS-SR-16). However, change in mean scores from baseline to week 6 was not significantly different between groups (mean difference = -2.0, 95% CI: -5.0 to 0.9).[19] A decrease in QIDS-SR-16 by at least 50% occurred in 21/30 (70%) and 14/29 (48%) of the psilocybin and escitalopram groups, respectively. Remission (defined as QIDS-SR-16 score <5) occurred in 57% in the psilocybin group and 28% in the escitalopram group. However, neither response nor remission rates were significantly different between groups.[19]

A 2023 meta-analysis of nine trials compared high dose psilocybin (25mg), moderate dose (10mg) or weight-based dose (0.215mg/kg) to low dose psilocybin (1mg) or placebo. Dichotomous data favored psilocybin use. The likelihood of psilocybin intervention leading to a treatment response was two times greater (RR: 2.02. 95% CI: 1.33 to 3.07) than placebo (I^2= 26%, p=0.23).[20] The likelihood of psilocybin leading to a remission of depression was also greater (RR: 2.71, 95% CI: 1.75 to 4.20), (I^2= 0.0%, p=0.53).[20] As for continuous data, change in depression scores was greater with psilocybin versus placebo or low dose psilocybin. The overall Hedges' g (1.64, 95% CI: 0.55 to 2.73) indicates a large effect size favoring psilocybin.

Another meta-analysis of nine studies (n=596) analyzing psilocybin 25mg, 10mg, 1mg, and weight-based psilocybin for MDD and depression associated with life threatening cancer also showed change in depression scores favoring psilocybin.[21] The findings suggested that psilocybin-assisted therapy may be effective for those not responding to conventional pharmacotherapy.[21] Though the optimal dose of psilocybin remains unclear, one study suggested that the 25mg dose had a significant antidepressant effect over lower doses.[21,22] There were no studies on psilocybin for PTSD. More robust evidence supporting psilocybin for use in Alcohol Use Disorder and Tobacco Use Disorder is needed.

Findings:

Methodological limitations in current studies restrict confidence in published findings. Participants were predominantly healthy white middle-aged adults, there was lack of standardization regarding psilocybin dosing (weight-based vs. moderate or high) and psychological support, and insufficient treatment blinding. Additionally, the inclusion of observational studies and studies with low sample sizes decreased certainty regarding the validity of results.

Therapeutic doses of psilocybin appear to produce tolerable acute AEs that resolve within 24-48 hours.[14] Unsupervised psilocybin use is not recommended as psychotherapy appears to be a key component in integrating the psilocybin experience with the physical and psychological processes, and most studies included psychotherapy.[11] Existing studies suggest that psilocybin may have therapeutic potential in mental health particularly in treating MDD and TRD, but further studies with large sample sizes and more standardized approaches are needed. Currently, psilocybin-assisted therapy is resource intensive requiring a considerable investment in staffing, time, and finances which present barriers to access.[21]

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

1. Lowe H, Toyang N, Steele B, et al. The Therapeutic Potential of Psilocybin. Molecules. 2021;26(10):2948.
2. MacCallum C, et al. Therapeutic use of psilocybin: Practical considerations for dosing and administration. Front Psychiatry. 2022;13:1040217.
3. Davis M. State Policies Supporting Evidence-Based Therapeutic Psilocybin Use. ASTHO. Published June 22, 2023. Accessed 7/6/2024.
4. The Royal Australian and New Zealand College of Psychiatrists. Psychedelics. Accessed 7/21/2024.
5. Government of Canada. Psilocybin and psilocin (Magic Mushrooms). Accessed 7/23/2024.
6. Guss J, Krause R, Sloshower J. The Yale Manual for Psilocybin-Assisted Therapy of Depression. PsyArXiv. August 2020. Accessed 7/23/2024.
7. Nichols D. Psilocybin: from ancient magic to modern medicine. J Antibiot. 2020;73(10): 679-86.
8. National Institute on Drug Abuse. Psilocybin (Magic Mushrooms). Published January 2024. Accessed July 21, 2024.

9. Shah F, Shehzadi S, Akram F, et al. Unveiling the Psychedelic Journey: An Appraisal of Psilocybin as a Profound Antidepressant Therapy. Mol Biotechnol. Published December 20, 2023.
10. Smausz R, Neill J, Gigg J. Neural mechanisms underlying psilocybin's therapeutic potential – the need for preclinical in vivo electrophysiology. J. Psychopharmacol. 2022;36(7):781-793.
11. Abbas A, et al. Oregon Psilocybin Advisory Board Rapid Evidence Review and Recommendations. Oregon Psilocybin Advisory Board. July 2021.
12. Oregon Health Authority. Center for Health Protection Oregon Psilocybin Services. Client Information Form. Accessed 6/24/2024.
13. Dahmane E, Hutson P, Gobburu J, et al. Exposure-Response Analysis to Assess the Concentration-QTc Relationship of Psilocybin/Psilocin. Clin Pharmacol Drug Dev. 2021;10(1):78-85.
14. Yerubandi A, Thomas J, Bhuiya N, et al. Acute Adverse Effects of Therapeutic Doses of Psilocybin. A Systematic Review and Meta-Analysis. JAMA. 2024;7(4):e245960.
15. Passie T, Juergen S, Schneider U, et al. The pharmacology of psilocybin. Addict Biol. 2002;(7);357-64.
16. Rosenblat J, Husain M, Lee Y, et al. The Canadian Network for Mood and Anxiety Treatments Task Force Report: Serotonergic Psychedelic Treatments for Major Depressive Disorder. Can J Psychiatry. 2023;68(1):5-21.
17. Mackey K, Anderson J, Williams B, et al. Evidence Brief: Psychedelic Medications for Mental Health and Substance Use Disorders. Washington DC: Evidence Synthesis Program, Health Synthesis Program, Department of Veterans Affairs. VA ESP Project #09-199;2022.
18. Davis A, Barrett F, May D, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder. JAMA Psychiatry. 2021;78(5):481-9.
19. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of Psilocybin versus Escitalopram for Depression. NEJM. 2021;384(15):1402-11.
20. Metaxa A, Clarke M. Efficacy of psilocybin for treating symptoms of depression: systematic review and meta-analysis. BMJ. 2024; 385:e078084.
21. Haikazian S, Chen-Li D, Johnson D, et al. Psilocybin-assisted therapy for depression. Psychiatry Res. 2023; 329:115531.
22. Goodwin G, Aaronson S, et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *NEJM.* 2022; 387:1637-48.
23. Varker T, Watson L, Gibson K, et al. Efficacy of psychoactive drugs for the treatment of posttraumatic stress disorder: A Systematic Review of MDMA, ketamine, LSD, and psilocybin. *J Psychoactive Drugs*. 2021;53(1):85-95.