MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Psilocybin Implications for Future Depression Therapy

by Anas Abuzoor, 2023 PharmD Candidate, Mikayla Bell, 2023 PharmD Candidate, Ami Leigh Schmidt, 2023 PharmD Candidate, Mahadi Zraik, 2023 PharmD Candidate, Sochenda Pen, 2024 PharmD Candidate, Kevin Bozymski, PharmD, BCPS, BCPP

In 2020, more than 20 million adults and 4 million adolescents in the United States had at least one major depressive episode.[1] Depression is a common yet serious mood disorder that negatively affects the way an individual feels, thinks, and acts. Depression, or major depressive disorder, is diagnosed after an individual experiences a 2-week period of depressed mood or loses interest or pleasure in daily activities along with additional symptoms such as changes in weight or sleep, fatigue, psychomotor agitation, feelings of worthlessness or guilt, decreased concentration, or thoughts of death or suicide.[2] It can lead to a variety of emotional and physical problems and can decrease a person's ability to function at home and work.

The American Psychiatry Association 2019 guidelines recommend psychotherapy as the first-line treatment for mild to moderate depression with supplementation from pharmacotherapy as needed for successful treatment.[3] Current Food & Drug Administration-approved pharmacotherapy for depression in adults includes tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRI), selective serotonin/norepinephrine reuptake inhibitors, and other options with unique mechanisms (Table 1). Unfortunately, traditional antidepressants are often limited by adverse effects, efficacy for only a subset of patients with depression, and poor adherence. It is common for patients to trial several antidepressant medications before finding benefit with limited adverse effects. As many as 50% of patients receive only a partial response while an additional 30% may be treatment resistant.[4] Additionally, the onset of action for antidepressants ranges from 6 to 12 weeks which can be discouraging for patients who are eager for symptom relief; this often results in medications being discontinued before their full benefits would be seen.[5,6]

The variability in effectiveness of current antidepressant medications is rooted in the deficit of knowledge of the pathophysiology of depression with a multitude of theories available based upon current treatment options. The most common monoamine theory explains depression as resulting from lower synaptic concentration of serotonin, norepinephrine, and dopamine, as the use of reserpine (a monoamine-depleting agent) causes depression symptoms.[7] However, this theory does not explain the therapeutic lag associated with reuptake inhibitor antidepressants or how alternative depression pharmacotherapies act by other mechanisms. Other theories explore the possibility of changes in receptor density affecting neurotransmitter levels; downregulation of brain-derived neurotrophic factor (BDNF) which plays a role in synaptic plasticity and neuron survival; shrinkage of the hippocampus; and abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis. Antidepressants reverse these effects after long-term treatment due to the chronic activation of monoamine receptors which induces BDNF production and downregulation of the HPA axis.[7] With limitations of current depression treatment practices, exploring alternative options is

TABLE 1. Select FDA-Approved Pharmacotherapies for Major Depressive Disorder in Adults[3]

Category	Drug Class	Generic Names
First-Generation	Tricyclic Antidepressants (TCAs)	Amitriptyline Doxepin Imipramine Nortriptyline
	Monoamine Oxidase Inhibitors (MAOIs)	Isocarboxazid Phenelzine Selegiline Tranylcypromine
Second-Generation	Atypical Antidepressants	Bupropion Mirtazapine
	Selective Serotonin Re-Uptake Inhibitors (SSRIs)	Citalopram Escitalopram Fluoxetine Paroxetine Sertraline
	N-methyl-D-aspartate (NMDA) Receptor Antagonist	Esketamine
	Selective Serotonin/Norepinephrine Re-uptake Inhibitors (SNRIs)	Desvenlafaxine Duloxetine Levomilnacipran Venlafaxine
	Serotonergic Modulators	Nefazodone Trazadone Vilazodone Vortioxetine

imperative. One exploratory option includes psychedelics like psilocybin which have garnered interest in the research community as a possible therapeutic alternative. The objective of this article is to review the proposed mechanism of action, evidence, and clinical applications of psilocybin for treatment-resistant depression.

Pharmacologic Basis for Psilocybin

Psilocybin is a natural product containing tryptamine derived from certain species of mushrooms.[8] Historically, it has been used as a hallucinogen to induce altered states of consciousness and provide euphoria. For this reason, it was classified as a Schedule I substance in 1970 under the Controlled Substances Act, meaning any use and research of psilocybin's mechanism of action and potential therapeutic use in mental health disorders was stringently regulated and almost impossible.[8] However, the difficulty in treating mental illness has led to a resurgent interest in psychedelic research during the past decade, including substances such as psilocybin, lysergic acid diethylamide (LSD), and ketamine for various mood disorders. This resurgence of interest in psychedelic research is targeting mental health disorders, and recent psilocybin research has examined use for treatment-resistant depression.[9]

Psilocybin is structurally related to serotonin and exerts effects on 5-HT2A receptors in the prefrontal cortex.[8] Specifically, it activates neurons within the prefrontal cortex leading to altered cortical signaling. Multiple studies have shown a reduction in amygdala activity and changes in functional connectivity via neuroimaging observations after the use of psilocybin in major depressive disorder (MDD) and healthy patients.[10] These neurons affect perception and preconceived assumptions, potentially allowing a person to adapt and develop new insights or outlooks. In comparison, traditional antidepressants modulate the serotonin balance whereas psilocybin may alter brain structure leading to the potential to tackle treatment-resistant mental health disorders.[8] Moreover, only a small amount of psilocybin is renally excreted when used; therefore, dose adjustments are not required for people with any renal impairment.[11]

Preliminary Clinical Research Findings

Although psilocybin has the potential to alter neurons positively and may be of use in mental health disorders, we still lack evidence for its safety and efficacy. A 2016 open-label feasibility study found that psilocybin reduced Quick Inventory of Depressive Symptomatology (QIDS) scores one week (mean QIDS difference −11.8, 95% CI: −9.15 - −14.35, p = 0.002) after treatment lasting until three months (mean QIDS difference −9.2, 95% CI: −5.69 - −12.71, p = 0.003) after treatment while producing only transient side effects such as headache, nausea, and anxiety.[12] At six months similar statistically significant reductions in QIDS scores were found.[13] Davis et al. studied the effects of psilocybin in MDD over a four-week period.[4] Twenty-four participants received 20 mg of psilocybin at their first visit and 30 mg of psilocybin at the second visit supplemented by psychotherapy. The primary outcome was the change in GRID-Hamilton Depression Rating Scale (GRID-HAMD) score from baseline to post-intervention week one and week four. Seventeen of twenty-four (71%) participants had an improvement of greater than 50% in their GRID-HAMD score at week one (Cohen d = 2.3; 95% CI: 1.5-3.1, p <0.001) and week four (Cohen d = 2.3; 95% CI: 1.5-3.1, p <0.001) while 13 of 24 (54%) met criteria for remission. A 12 month follow-up found these results persisted after the second dose at 12 months with remission rates of up to 75% without serious adverse events.[14] This study demonstrated a quick onset for relief of depression symptoms while also producing lasting effects that persisted weeks after receiving psilocybin.

A six-week phase two randomized control trial compared the safety and efficacy of psilocybin and escitalopram for longstanding, moderate-to-severe major depressive disorder.[15] The first group (n = 30) was given two 25 mg doses of psilocybin three weeks apart plus a daily placebo pill. The participants in the second group (n = 29) were given two separate doses of 1 mg of psilocybin three weeks apart plus daily escitalopram 20 mg. The primary clinical outcome of the trial was the change from baseline in scores on the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16) after six weeks. Scores range from 0 to 27 with higher scores indicating more severe depression. The mean (± standard deviation) change from baseline in the score on the QIDS-SR-16 at week 6 was −8.0 (±1.0) in the psilocybin group and −6.0 (±1.0) in the escitalopram group (95% CI: -5.0-0.9, p = 0.17). Furthermore, the secondary outcomes demonstrated that psilocybin had resulted in a higher response rate on the QIDS-SR-16 (70% response with psilocybin versus 48% response with escitalopram) and remission rate (57% remission with psilocybin versus 28% remission with escitalopram). The psilocybin group reported improvements in perceived intense emotion, feeling compassion and pleasure, and ability to cry.[15] The most common adverse event in the psilocybin group was headaches within 24 hours. The escitalopram group reported more adverse events such as dry mouth, sexual dysfunction, anxiety, drowsiness, and reduced emotional response. A limitation of the study is the brief duration of escitalopram treatment, due to its delayed therapeutic action on depression and inability to correct for confounders which prevented the authors from demonstrating significance in their secondary outcomes. Direct comparisons between psilocybin and FDA-approved treatments for depression are lacking; therefore, larger and longer studies are needed.

Impact on Patient Care and Barriers to Use

Considering the recent interest in psilocybin use, it is important for healthcare professionals to consider its impact in a healthcare setting. Unfortunately, psilocybin has many unanswered questions regarding its underlying pharmacology and toxicology due to its regulatory status. Per the Registry of Toxic Effects of Chemical Substances, psilocybin is assigned a value of 641 on a scale where higher values correspond to better safety profiles (as compared to nicotine with a value of 21 and aspirin with a value of 199).[16] While this registry was last updated in January 1997, recent studies in non-human models have supported both low physiological toxicity and low abuse liability.

Individuals with current psychosis or those at risk for psychotic disorders

are thought to be at an increased risk for prolonged psychiatric reactions and have been excluded from studies thus far.[17] The major risk of administering psilocybin is the potential for a psychologically overwhelming anxious, fearful, or confused response which may lead to potentially dangerous behavior in unmonitored settings. For this reason, patient preparation, session monitoring, and follow-up discussions are implemented to minimize the risk of these occurrences. Other patient populations excluded from current trials include those at an elevated risk of cardiovascular problems due to psilocybin's risk of inducing a moderate increase in blood pressure. Further reports have been made of transient post-session headaches; however, history of headaches has not been an exclusion from participation.

Psilocybin is only approved by the FDA for investigational use, with no insurance coverage or patient accessibility outside of clinical trials.[18] Not only is psilocybin access restricted for patients, but investigators must follow strict rules as well. Investigators must register with the Drug Enforcement Administration (DEA), submit research protocols, and follow strict guidelines for obtaining, storing, and administering psilocybin. Currently, there are only two companies producing psilocybin used in advanced clinical trials: COMPASS Pathways in the United Kingdom and the Usona Institute in Fitchburg, Wis.[19,20] In addition to the legal criteria above, it can also be difficult to obtain funding. From 2015 to 2020, there were nearly 550 grants awarded for psychedelic research.[21] Although psilocybin is a federally classified Schedule I substance, psilocybin has been decriminalized in several cities, beginning in May 2019 with Denver, Colorado.[22] In November 2020, Oregon became the first state to legalize the use of psilocybin for medical purposes.[23]

Future Directions & Conclusion

Research regarding psilocybin for treatment-resistant depression and other mental health disorders is gaining traction, with certain doses showing promise for affecting brain function and structure positively without causing significant adverse effects. However, future studies, funding, and legal guidance are needed to determine the relative risks and benefits of long-term psilocybin use for these indications. Pharmacists and other health care professionals should continue monitoring this growing area of research to determine psilocybin's appropriate place in therapy.

Anas Abuzoor, Mikayla Bell, Ami Leigh Schmidt, and Mahadi Zraik are 2023 Doctor of Pharmacy Candidates at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Sochenda Pen is a 2024 Doctor of Pharmacy Candidates at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Kevin Bozymski is an Assistant Professor Department of Clinical Sciences at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI.

Acknowledgement: We thank Drs. Brooke Foster and Michael Nagy for providing feedback for the final manuscript.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

References

1. Substance Abuse and Mental Health Services Administration. Results from the 2020 national survey on drug use and health: summary of national findings. Published 2021. Accessed September 10, 2022. https://www.samhsa.gov/data/sites/default/files/reports/rpt35325/2020NSDUHFFRSlides090821.pdf
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington D.C.: 2013.
3. Guideline Development Panel for the Treatment of Depressive Disorders (2021). Summary of the clinical practice guideline for the treatment of depression across three age cohorts. *Am Psychol.* 2022;77(6):770-780. doi:10.1037/amp0000904
4. Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial [published correction appears in *JAMA Psychiatry*. 2021 Feb 10]. *JAMA Psychiatry.* 2021;78(5):481-489. doi:10.1001/jamapsychiatry.2020.3285
5. Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry.* 2007;68(suppl 8):17-25.
6. DeBattista C. Antidepressant agents. In: Katzung BG. eds. Basic & Clinical Pharmacology, 14e. McGraw Hill; 2017. Accessed August 30, 2022.
7. VandenBerg AM. Major depressive disorder. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. eds. Pharmacotherapy: A Pathophysiologic Approach, 11e. McGraw Hill; 2020. Accessed August 30, 2022.
8. Nutt D, Erritzoe D, Carhart-Harris R. Psychedelic psychiatry's brave new world. *Cell.* 2020;181(1):24-28. doi: 10.1016/j.cell.2020.03.020
9. Ziff S, Stern B, Lewis G, Majeed M, Gorantla VR. Analysis of psilocybin-assisted therapy in medicine: a narrative review. *Cureus.* 2022;14(2):e21944. doi:10.7759/cureus.21944
10. Gill H, Puramat P, Patel P, et al. The effects of psilocybin in adults with major depressive disorder and the general population: findings from neuroimaging studies. *Psychiatry Res.* 2022;313:114577. doi:10.1016/j.psychres.2022.114577
11. Brown RT, Nicholas CR, Cozzi NV, et al. Pharmacokinetics of escalating doses of oral psilocybin in healthy adults. *Clin Pharmacokinet.* 2017;56(12):1543-1554. doi:10.1007/s40262-017-0540-6
12. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry.* 2016;3(7):619-627. doi:10.1016/S2215-0366(16)30065-7
13. Carhart-Harris RL, Bolstridge M, Day CMJ, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl).* 2018;235(2):399-408. doi:10.1007/s00213-017-4771-x
14. Gukasyan N, Davis AK, Barrett FS, et al. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: prospective 12-month follow-up. *J Psychopharmacol.* 2022;36(2):151-158. doi:10.1177/02698811211073759
15. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of psilocybin versus escitalopram for depression. *N Engl J Med.* 2021;384(15):1402-1411. doi:10.1056/NEJMoa2032994
16. RTECS, Registry of Toxic Effects of Chemical Substances. [Atlanta, Ga.]: U.S. Dept. of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, 1997.
17. Kargbo RB. Psilocybin therapeutic research: the present and future paradigm. *ACS Med Chem Lett.* 2020;11(4):399-402. Published March 2, 2020. doi:10.1021/acsmedchemlett.0c00048
18. Hale V. The FDA and psychedelic drug development: working together to make medicines. Multidisciplinary Association for Psychedelic Studies Bulletin. 2020;30(1):27-29.
19. Investigational Drug & Material Supply Program. Usona Institute. Accessed August 30, 2022. usonainstitue.org
20. About psilocybin therapy. COMPASS Pathways. Accessed August 30, 2022. compasspathways.com
21. Lowe H, Toyang N, Steele B, et al. The therapeutic potential of psilocybin. *Molecules.* 2021;26(10):2948. doi:10.3390/molecules26102948
22. Denver, CO., Code of Ordinances ch 28 § 302 (2020). Accessed September 13, 2022. https://library.municode.com/co/denver/codes/code_of_ordinances?nodeId=TITIIREMUCO_CH28HURI_ARTXPUSAENPREN_S28-302ENPRSIMU
23. Chapter 475A. www.oregonlegislature.gov. Published 2021. Accessed September 8, 2022. https://www.oregonlegislature.gov/bills_laws/ors/ors475a.html

Patient safety. Professional practice. Community impact.

PTCB
Pharmacy Technician Certification Board®

Build your team with confidence.

Employers who rely on PTCB consistently report improved employee performance, greater efficiency, lower turnover, and reduced time and expense to train and advance pharmacy technicians.

Assessment-Based Certificates

BILLING AND REIMBURSEMENT
CONTROLLED SUBSTANCES DIVERSION PREVENTION
HAZARDOUS DRUG MANAGEMENT
IMMUNIZATION ADMINISTRATION
MEDICATION HISTORY
MEDICATION THERAPY MANAGEMENT
POINT-OF-CARE TESTING
REGULATORY COMPLIANCE*
SUPPLY CHAIN AND INVENTORY MANAGEMENT*
TECHNICIAN PRODUCT VERIFICATION (TPV)

*Planned for 2022

Certifications

CPhT
Certified Pharmacy Technician (CPhT)

CSPT
Compounded Sterile Preparation Technician® (CSPT®) Certification

CPhT-Adv
Advanced Certified Pharmacy Technician (CPhT-Adv) Certification

View PTCB's full suite at ptcb.org/credentials