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Risks of using psilocybin in treatment of treatment-resistant depression

Michał Orzechowski
Jędrzej Śniadecki Specialist Hospital in Nowy Sącz
ul. Młyńska 10, 33 – 300 Nowy Sącz, Poland
https://orcid.org/0009-0009-9315-1361
michal.k.orzechowski@outlook.com

Joanna Orzechowska
Jędrzej Śniadecki Specialist Hospital in Nowy Sącz
ul. Młyńska 10, 33 – 300 Nowy Sącz, Poland
https://orcid.org/0009-0005-6594-3717
joannasapala99@gmail.com

Paulina Fijałek

Southern Hospital, Rotmistrza Witolda Pileckiego 99, 02-781 Warsaw, Poland

https://orcid.org/0009-0000-2508-7059

paulina.fijalek@gmail.com

Jan Karczmarz
Southern Hospital, Rotmistrza Witolda Pileckiego 99, 02-781 Warsaw, Poland
https://orcid.org/0009-0004-4960-4013
jasiekkarczmarz@wp.pl

Aleksandra Paprocka
Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wroclaw, Poland
https://orcid.org/0009-0004-2082-5541
aleksandrapapr@gmail.com
Marika Gutowska
Józef Struś Multi-Specialist Municipal Hospital, Szwajcarska 3, 61-285, Poznań, Poland
https://orcid.org/0009-0004-8297-5465
marikagutowska99@gmail.com

Agnieszka Kosińska
District Hospital in Chrzanow, Topolowa 16, 32-500 Chrzanow, Poland
https://orcid.org/0009-0008-3041-274X
agnieszka0kosinska@gmail.com

Urszula Świrk
Independent Public Health Care Facilities in Przasnysz, Dr. Wojciech Oczko Hospital.
https://orcid.org/0009-0007-6756-6016
ula.swirk@gmail.com

Wiktoria Belcarz
Murcki Hospital Sp. z o.o., Sokołowskiego 2, 40-749 Katowice, Poland
https://orcid.org/0009-0003-3748-9380
wbelcarz@poczta.fm

Karolina Kalinowska
Health Care Team of the District Hospital In Sochaczew, Batalionów Chłopskich 3/7,96-500 Sochaczew, Poland
https://orcid.org/0009-0007-2657-7165
karolina1119@gmail.com

Abstract:

Introduction

As depression rates continue to rise globally, the need for more effective and innovative treatments has become increasingly urgent, highlighting the potential impact of psilocybin as a promising therapeutic option. However, to ensure its safe and effective integration into clinical practice, it is essential to establish robust safety parameters for its administration. This paper focuses on addressing the risks associated with psilocybin therapy. We believe this paper can help understand risks as a platform for safety based treatment.

Material and Methods

A comprehensive literature search was conducted using the PubMed and Google Scholar databases, supplemented by references cited in the initially identified articles. The search focused on studies and reviews addressing the challenges and risks associated with psilocybin use in the treatment of treatment-resistant depression (TRD).

Keywords psilocybin, treatment-resistant depression, adverse effects, safety, and psychedelic therapy.

Introduction:

Psilocybin, a serotonergic hallucinogen derived from certain fungi, has gained significant attention for its potential in treating treatment-resistant depression (TRD). Its mechanism of action includes modulation of serotonin receptors, promotion of neuroplasticity, and enhancement of emotional processing. While its therapeutic promise is compelling, the safety profile of psilocybin warrants careful examination. Adverse effects, such as transient anxiety, mood fluctuations, and psychotic-like episodes, are commonly reported during treatment, posing challenges to its clinical implementation. Additionally, psilocybin can cause temporary increases in blood pressure, which may pose risks for individuals with cardiovascular conditions, particularly untreated hypertension. Rare but serious adverse events, including suicidal ideation and self-harm during follow-up periods, further highlight the importance of robust monitoring and support. This article aims to provide a comprehensive analysis of the risks associated with psilocybin therapy for TRD, focusing on understanding the mechanisms underlying these adverse effects and their clinical implications. A review of existing studies reveals that while most side effects are mild and transient, individual variability in response and long-term safety concerns remain significant challenges. By addressing these issues, we aim to support clinicians and patients in making informed decisions regarding the use of psilocybin in treating TRD, ensuring its benefits are maximized while minimizing potential risks.

Purpose of the study:

The Aim of the study:

The aim of this study is to review and synthesize the existing literature on the pharmacological properties, mechanisms of action, and clinical applications of psilocybin in the treatment of treatment-resistant depression. Through this comprehensive analysis, the study seeks to provide a clearer understanding of psilocybin's therapeutic potential while highlighting the unique challenges and risks associated with its use. Treatment-resistant depression remains a significant clinical challenge, often leading to limited options for patients who have not responded to conventional therapies. As a novel therapeutic agent, psilocybin has gained attention for its ability to modulate serotonin pathways and elicit profound psychological effects, yet its usage is not without risks, including potential psychological distress, adverse reactions, and the ethical concerns surrounding its administration in vulnerable populations. This study intends to delve into these issues, exploring not only the promising mechanisms by which psilocybin exerts its antidepressant effects but also the broader safety profile, regulatory issues, and implications of its use in this context. By synthesizing current evidence, the research aims to present a balanced perspective that considers both the potential benefits and the risks of integrating psilocybin into treatment paradigms for depression.

Materials and methodology:

To explore the challenges and risks of using psilocybin in the treatment of treatment resistant depression, literature was collected through comprehensive searches in the PubMed and Google Scholar databases, supplemented by references cited in the initially retrieved articles.

The materials and methodology of this study involved a systematic approach to reviewing the risks and challenges associated with the use of psilocybin in the treatment of treatment-resistant depression. A comprehensive literature search was conducted using two primary databases, PubMed and Google Scholar, to ensure a wide and diverse range of peer-reviewed studies, clinical trials, and meta-analyses were included. Additionally, the search process was augmented by manually reviewing the reference lists of initially retrieved articles to identify

any pertinent studies that may not have been captured in the database search. By adopting a systematic approach, the study aims to provide a balanced and evidence-based perspective on this area of psychiatric treatment.

History of psilocybin

Psilocybin has a long and fascinating history that can be traced back to the 16th century, when Spanish Franciscan friar Bernardino de Sahagún chronicled its use among the Aztecs in his ethnographic research. His work, compiled in the *General History of the Things of New Spain*, described the ceremonial use of sacred mushrooms, referred to as teonanacatl, meaning "God's Flesh." These fungi held immense cultural and spiritual significance, serving as a cornerstone of religious rituals and practices in Mesoamerican societies. Sahagún's writings provide one of the earliest known records of psilocybin mushrooms in human history. However, despite his meticulous documentation, the psychoactive properties of these mushrooms remained the subject of controversy and skepticism for centuries, largely due to their limited visibility in Western scientific discourse and ethnobotanical studies. (1)

The scientific exploration of psilocybin mushrooms began to take shape in the 20th century. In 1936, the ethnobotanist Roberto Weitlaner collected specimens from the Mazatec region of Mexico. Unfortunately, the samples were too decomposed for accurate taxonomic identification, leaving the true nature of these fungi uncertain. It was not until Harvard botanist Richard Evans Schultes' work in the 1930s and 1940s that significant progress was made. Schultes identified several species, including *Psilocybe caerulescens* and *Psilocybe cubensis*, marking an important step in the scientific understanding of these mushrooms. Although this momentum was briefly halted by the disruptions of World War II, it resumed in the 1950s with groundbreaking contributions from R. Gordon Wasson, a banker and passionate amateur mycologist, and his wife, Valentina Wasson. Together, they documented their experiences with the Mazatec curandera Maria Sabina, who introduced them to the traditional ceremonial use of psilocybin mushrooms. Their work gained global attention after it was featured in *Life Magazine*, sparking widespread interest in the cultural and psychoactive aspects of these fungi. This newfound recognition fueled further scientific inquiry by figures such as Roger Heim, who collaborated with Wasson to classify additional psilocybin species, and Albert Hofmann, who succeeded in isolating and synthesizing psilocybin for the first time. These developments laid the foundation for the modern exploration of psilocybin's potential therapeutic applications, transforming what was once a sacred Mesoamerican tradition into a subject of cutting-edge biomedical research. (2)

Background of depression

Depression is a complex clinical syndrome characterized by a cluster of symptoms that affect emotional, cognitive, and physical functioning. The disorder is recognized in major diagnostic systems such as the ICD-10 and DSM-IV, which provide standardized criteria for diagnosis. Both classifications define depression syndromally, focusing on a set of co-occurring symptoms rather than a single identifiable cause. These symptoms include persistent low mood, loss of interest or pleasure (anhedonia), fatigue, impaired concentration, and feelings of worthlessness, among others. For major depressive disorder (MDD), the DSM-IV requires the presence of at least five symptoms over a minimum duration of two weeks, with one being either low mood or anhedonia. (3,4)

Depression is influenced by both genetic and environmental factors. A key part of its development involves dysfunction in three brain chemical systems: serotonin (5HT), norepinephrine (NE), and dopamine (DA). Among these, serotonin plays a major role. Studies show that people with depression often have reduced serotonin activity, seen in lower serotonin

transporter (SERT) levels and fewer serotonin receptors in certain brain regions. These transporters and receptors are crucial for regulating serotonin, which affects mood. Treatments like selective serotonin reuptake inhibitors (SSRIs) target this system. However, when serotonin levels are deliberately lowered—such as through tryptophan depletion—patients who have recovered from depression often experience a quick return of symptoms, further supporting serotonin's importance. Genetic factors also play a role. For example, people with the "s" allele of the SERT gene (SLC6A4) are more vulnerable to the effects of early-life stress, like childhood trauma, which increases their risk of depression. This gene variation results in reduced ability to regulate serotonin levels in the brain. (5,6)

Dopamine (DA) dysfunction also make its stand in the pathophysiology of depression, complementing the established roles of serotonin and norepinephrine. While dopamine is most commonly associated with disorders like schizophrenia, growing evidence suggests its involvement in depression, particularly in cases where standard treatments, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), fail to achieve full remission. This has led to the development of the "dopamine hypothesis" of depression. A key symptom of depression, anhedonia which is the inability to experience pleasure strongly implicates role of dopamine systems. Dopamine is essential for pleasure and reward processing, including behaviours like eating, socializing, and sexual activity. Studies, including postmortem and PET imaging, have shown decreased dopamine transporter availability and increased dopamine receptor density in patients with depression, suggesting reduced synaptic dopamine levels. These findings highlight the potential of therapies targeting dopamine, such as monoamine oxidase inhibitors (MAOIs), dopamine receptor agonists, or investigational drugs that enhance serotonin, norepinephrine, and dopamine simultaneously (triple reuptake inhibitors). Additionally, depression is a multifaceted disorder, and other neurotransmitter systems, such as glutamate, γ-aminobutyric acid (GABA), and brain-derived neurotrophic factor (BDNF), may also contribute to its development. Hormonal systems like corticotropin-releasing factor (CRF) and thyrotropin-releasing hormone have also been implicated, further emphasizing the complexity of depression and the need for diverse treatment approaches. (7,8)

Epidemiology of treatment resistance depression

Treatment-resistant depression (TRD) represents a clinical challenge in psychiatry, affecting a substantial proportion of individuals diagnosed with major depressive disorder (MDD) who fail to achieve remission despite receiving guideline-recommended pharmaceutical interventions. TRD is commonly defined as the failure to respond satisfactorily to at least two different antidepressant medications, each administered at an adequate therapeutic dose and duration of no less than four weeks. This definition aims to ensure that the diagnosis captures genuine resistance to pharmacological treatment rather than issues related to poor adherence or insufficient dosage. Recent epidemiological studies utilizing extensive U.S.-based healthcare datasets, such as the Humana and Optum databases, have provided valuable insights into the prevalence and demographic distribution of TRD. (9)

Within the population of pharmaceutically treated depression (PTD) patients, the prevalence of TRD has been found to approximate 6%, with slight variations depending on the dataset and the statistical adjustments applied. Specifically, analyses revealed prevalence estimates of 6.8% in the Humana database and 5.8% in the Optum database when adjusted for factors such as age and gender. These findings underscore the considerable burden of TRD among patients already engaged in conventional treatment pathways. From a demographic perspective, certain groups appear disproportionately affected. TRD is more frequently observed in females compared to males, potentially reflecting gender differences in both depression prevalence and treatment

responses. Additionally, middle-aged adults, particularly those aged 45–64 years, exhibit higher rates of TRD, which may relate to cumulative stressors or changes in neurobiological systems during this life stage. Ethnic disparities are also evident, with White patients showing higher TRD prevalence than other racial or ethnic groups, raising important questions about potential sociocultural or biological contributors to treatment outcomes. (9)

Overview of Psilocybin and Its Mechanisms of Action

Psilocybin is a naturally occurring chemical compound found in certain species of fungi and belongs to the tryptamine group of classic serotonergic hallucinogens (10). Chemically known as 4-phosphoryloxy-N,N-dimethyltryptamine (4-PO-DMT), psilocybin functions as a prodrug, being metabolized in the body into its active form, psilocin (4-hydroxy-N,N-dimethyltryptamine or 4-OH-DMT) (11). Psilocin binds to 5-HT2A receptors, a specific subtype of serotonin receptor widely distributed in the brain, which are critical in modulating mood, cognition, and memory (11). This interaction plays a fundamental role in psilocybin's therapeutic potential, particularly its ability to desensitize 5-HT1A and 5-HT2A receptors, thereby contributing to its antidepressant effects in conditions such as treatment-resistant depression (12). Beyond its effects on serotonin pathways, psilocybin also modulates other neurotransmitter systems, including glutamate and dopamine, particularly in the prefrontal cortex, a brain region involved in emotional and cognitive regulation (12). Additionally, psilocybin has been shown to influence neuroplasticity, promoting structural and functional changes in the brain. By inducing glutamate release and activating AMPA receptors, psilocybin stimulates the secretion of brain-derived neurotrophic factor (BDNF) and the mechanistic target of rapamycin (mTOR) signaling pathway. This cascade promotes synaptogenesis and enhances neuroplasticity, offering potential mechanisms for its long-lasting therapeutic effects (13). Together, these pharmacological properties underscore the compound's ability to modulate both neurochemical and structural components of the brain, which may explain its promising role in treating mood disorders like treatment-resistant depression. However, these mechanisms also highlight the complexity of psilocybin's effects and the need for a deeper understanding of its risks and long-term implications.

Long-term effects on behavioural change

The long-term effects of psilocybin, particularly its ability to drive enduring behavioral and personality changes, have become a focal point in clinical research due to their profound implications for mental health treatment. Psilocybin-assisted therapy has been consistently associated with sustained increases in the personality trait of Openness, which is linked to creativity, imagination, and a heightened receptiveness to novel experiences. This is particularly notable because personality traits, especially in adulthood, are typically stable and exhibit only gradual changes over time (14). Studies attribute these lasting changes to the profound psychological experiences induced by psilocybin, often referred to as peak or mystical experiences. These events, characterized by a deep sense of unity, transcendence, and profound insight, have been strongly correlated with positive clinical outcomes, including reductions in Neuroticism, enhanced emotional well-being, and improved interpersonal relationships (14, 15). In a 14-month follow-up study, the majority of participants identified their psilocybin experience as one of the most meaningful and spiritually significant events in their lives, with 64% reporting sustained improvements in life satisfaction, mood, and overall well-being (15). The effects were significantly more pronounced than those observed with other psychoactive substances, such as methylphenidate, underscoring the unique transformative potential of psilocybin when administered in controlled and supportive environments. These long-term benefits are believed to stem from psilocybin's ability to facilitate profound introspection and emotional breakthroughs, promoting shifts in attitudes and altruistic behaviors. Moreover, the

therapeutic potential of these transformative experiences extends beyond depression, offering promising avenues for addressing addiction, existential distress in terminal illnesses, and broader aspects of psychological and spiritual growth. However, while the lasting behavioral and personality changes reported in these studies are promising, they also emphasize the need for cautious application, robust ethical frameworks, and further research to fully understand the risks and implications of such profound alterations in personal identity and outlook. (15)
Psilocybin has demonstrated remarkable potential for facilitating long-term behavioral changes, particularly in addressing substance use disorders such as alcohol dependence and smoking addiction. In the context of alcohol dependence, a study involving ten participants diagnosed with DSM-IV alcohol dependence reported significant reductions in heavy drinking days and overall drinking days following psilocybin-assisted therapy (16). These improvements were most pronounced after the initial psilocybin session and were maintained throughout the follow-up period, with effect sizes ranging from Cohen's $d = 0.75$ to 1.38, indicating substantial clinical impact (16). Key to these outcomes was the integration of psilocybin administration with motivational enhancement therapy (MET), which provided a structured and supportive environment, enabling participants to process their transformative experiences. These experiences often led to improved emotional regulation and reduced dependency, forming the basis for enduring behavioral change (16). Similarly, psilocybin has shown efficacy in smoking cessation therapy, with long-term abstinence rates significantly higher than traditional methods. In a study of 15 participants, 80% achieved verified smoking abstinence at a 6-month follow-up, attributing their success to profound shifts in perspective facilitated by psilocybin sessions (17). Participants frequently described changes in life priorities and enhanced confidence in their ability to quit smoking, which were strongly associated with the mystical experiences induced by psilocybin. These experiences, often rated among the most meaningful of their lives, appeared to bolster motivation, reduce cravings, and diminish withdrawal symptoms over time (17). Biological markers such as reductions in breath carbon monoxide and urine cotinine levels corroborated these findings, further emphasizing psilocybin's role in catalyzing meaningful behavioral change. While these studies highlight psilocybin's potential to promote long-term shifts in behavior, their small sample sizes and homogeneous populations underscore the need for larger, more diverse trials to confirm efficacy, refine therapeutic protocols, and explore mechanisms underlying these transformative effects (16, 17).

Risks associated with psilocybin therapy

As psilocybin therapy continues to attract attention as a promising intervention for treatment-resistant depression, it is imperative to thoroughly examine its associated risks to ensure safe and effective use. In the "Goodwin" trial, a high dose of psilocybin (25 mg) was administered to a cohort of 79 participants, providing valuable insights into both the short- and long-term adverse effects of the compound. On the first day following administration, participants frequently reported symptoms such as headache, nausea, dizziness, fatigue, mood changes, anxiety, insomnia, and paraesthesia. While these symptoms were typically transient and diminished significantly over the following weeks, they nonetheless underline the need for supportive care during the acute phase of treatment. Importantly, no serious adverse events occurred on the day of administration. However, a concerning observation was the emergence of suicidal ideation and intentional self-injury between days 2 and 3 weeks post-treatment, suggesting that patients undergoing psilocybin therapy may be vulnerable to emotional and psychological disturbances in the subacute phase. Additionally, during the period from weeks 3 to 12, isolated cases of headaches, suicidal behaviours, and one instance of drug withdrawal syndrome related to codeine were recorded. Interestingly, when two lower-dose groups (10 mg, n=75; 1 mg, n=79) were evaluated, adverse events were less frequent compared to the high-

dose group, though there was a slightly increased incidence of mild side effects during the 3–12-week period, emphasizing the complexity of psilocybin's dose-dependent risk profile (18).
In a smaller trial involving fewer participants, the risks were similarly observed to be primarily mild and transient. Adverse events included anxiety during the drug onset phase (n=12), confusion or thought disorder (n=9), nausea (n=4), and headache (n=4). Subacute headaches typically resolved within 1–2 days, and paranoia, reported by one participant, was mild and transient. Crucially, no prolonged psychotic symptoms were documented in the study. Nevertheless, one participant experienced worsening depression during the 3-month follow-up period, necessitating referral for further care by a general practitioner. This case underscores the need for long-term follow-up in patients receiving psilocybin, as delayed-onset adverse effects may emerge even after initial treatment appears successful (19).
Additionally, psilocybin therapy presents distinct physical risks, particularly for individuals with pre-existing cardiovascular conditions. A study by Felix Hasler et al. demonstrated a transient but notable increase in blood pressure following psilocybin administration. This finding is of particular relevance for individuals with untreated hypertension or other cardiovascular vulnerabilities, as the acute cardiovascular response to psilocybin could potentially exacerbate underlying conditions, leading to severe complications if left unmonitored. As a result, it is strongly recommended that patients with hypertension or cardiovascular disease undergo thorough medical evaluation and continuous monitoring during psilocybin therapy, and in some cases, the use of psilocybin may need to be contraindicated altogether (20).

Discussion

To date psilocybin shows great potential in managing treatment-resistant depression It is of great importance to understand and deepen knowledge about safety parameters. Psilocybin has been reported to have most favourable safety profile of all psychedelics. The "Goodwin" trial highlights the spectrum of adverse effects associated with psilocybin, including headaches, nausea, and psychological symptoms such as anxiety and mood changes, which were generally transient and diminished over time. However, the documentation of severe outcomes like suicidal ideation and self-injury weeks post-administration in high-dose groups underscores the importance of ongoing monitoring. Lower-dose groups exhibited fewer severe events, yet an increased frequency of adverse effects in later weeks suggests that even low-dose therapy requires sustained vigilance. Smaller trials similarly report mostly mild and transient adverse effects, with one case of worsening depression requiring additional care, emphasizing the need for individualized risk assessment.
Physical risks, such as the transient hypertensive response noted in Felix Hasler et al.'s study, highlight the potential dangers for individuals with untreated cardiovascular conditions, necessitating careful pre-screening and medical supervision during therapy.
To enhance the safety and feasibility of psilocybin therapy, it is imperative to establish comprehensive guidelines. These should include thorough pre-treatment evaluations to screen for psychiatric and cardiovascular vulnerabilities, tailored dosing regimens based on individual risk profiles, and protocols for close monitoring during and after administration to manage delayed adverse effects. Additionally, robust training programs for healthcare professionals on administering psilocybin therapy and managing its psychological and physical impacts can help mitigate risks. Developing standardized adjunctive therapies, such as psychological counselling during psilocybin use, may further enhance safety and therapeutic outcomes.
By addressing these safety considerations, psilocybin therapy can be made more accessible and viable, enabling its benefits to be harnessed while safeguarding patient health.

Summary

Psilocybin, a hallucinogenic compound classified as a serotonergic tryptamine, has garnered significant attention in recent years for its potential use in the treatment of treatment-resistant depression. Its mechanism of action is rooted in its metabolism into psilocin, the active form that primarily binds to 5-HT2A serotonin receptors in the brain. This interaction profoundly influences mood, cognition, and memory, which are critical in addressing the core symptoms of depression. Psilocybin's antidepressant effects are mediated through the desensitization of 5-HT1A and 5-HT2A receptors, which are central to mood regulation. However, its effects are not limited to serotonin modulation; psilocybin also impacts other neurotransmitter systems, particularly glutamate and dopamine, within the prefrontal cortex, an area of the brain crucial for executive function and emotional processing. Beyond neurotransmitter modulation, psilocybin has been shown to promote neuroplasticity by triggering the release of glutamate, which subsequently activates AMPA receptors and stimulates pathways such as BDNF (brain-derived neurotrophic factor) and mTOR (mechanistic target of rapamycin). These pathways are pivotal for synaptogenesis, the formation of new synaptic connections, which could underlie psilocybin's ability to foster lasting improvements in emotional and cognitive health.

Despite its promise, the use of psilocybin in a therapeutic setting is not without risks. Clinical trials, including the "Goodwin" study, have reported a range of transient side effects associated with psilocybin administration, particularly at higher doses. These include headaches, nausea, and heightened anxiety during the acute phase of treatment, which typically lasts several hours. More concerning, however, is the minority of cases where patients experienced severe outcomes, such as suicidal ideation, sometimes occurring weeks after treatment . Although lower doses appear to reduce the likelihood of such severe adverse effects, careful patient monitoring remains essential. Cardiovascular risks also pose a significant challenge. Psilocybin has been linked to transient elevations in blood pressure, making it particularly risky for individuals with preexisting cardiovascular conditions such as untreated hypertension. These risks highlight the necessity for robust safety protocols and comprehensive patient evaluations before initiating treatment.

To mitigate these risks, several strategies have been proposed. Pre-screening patients for psychiatric vulnerabilities, such as a history of psychosis or severe anxiety disorders, is critical to identify those who may be at higher risk of adverse psychological reactions. Similarly, thorough cardiovascular assessments are essential to rule out conditions that could be exacerbated by the transient physiological effects of psilocybin. Individualized dosing regimens, tailored to the patient's specific needs and medical history, have also been recommended to minimize the likelihood of adverse effects while optimizing therapeutic outcomes. Post-treatment monitoring is equally important, as some side effects, such as suicidal ideation, may manifest weeks after the acute treatment phase. Integrating psilocybin therapy with adjunctive psychological support, such as structured counselling or psychotherapy, can further enhance safety and efficacy by providing patients with the tools to process their experiences in a supportive environment. Additionally, training healthcare providers to manage the unique therapeutic and adverse effects of psilocybin is essential for its safe integration into clinical practice.

Although psilocybin represents a groundbreaking approach to addressing treatment-resistant depression, its use is accompanied by substantial challenges that necessitate a cautious and evidence-based approach. The combination of its complex pharmacological effects and potential risks underscores the need for multidisciplinary collaboration in research and clinical practice. By adhering to stringent safety protocols and integrating therapy within a broader psychological and medical framework, psilocybin could become a transformative tool in the

management of treatment-resistant depression, provided its risks are carefully managed and minimized.

Conclusions:
Psilocybin demonstrates considerable potential as a therapeutic option for treatment-resistant depression, leveraging its unique mechanisms to promote neuroplasticity and emotional processing. However, its clinical application is not without risks, emphasizing the need for careful consideration of safety parameters. Adverse effects, though often mild and transient, such as headaches, nausea, and anxiety, can escalate to more serious outcomes like suicidal ideation and self-injury, particularly with high doses. Even low-dose treatments require ongoing vigilance due to the potential for delayed adverse effects. Cardiovascular risks, including transient hypertension, further underscore the importance of comprehensive pre-treatment evaluations, particularly in patients with preexisting conditions.
To optimize the safety and efficacy of psilocybin therapy, it is essential to establish robust guidelines that include thorough screening for psychiatric and physical vulnerabilities, individualized dosing strategies, and rigorous post-administration monitoring. Additionally, equipping healthcare providers with specialized training and integrating psychological support into treatment protocols can mitigate risks and enhance patient outcomes. By addressing these safety considerations, psilocybin therapy can be responsibly incorporated into clinical practice, providing a valuable option for managing the complexities of treatment-resistant depression while prioritizing patient health and well-being.

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Michał Orzechowski, Jan Karczmarz
Methodology;
Wiktoria Belcarz
Software;
Magdalena Balwierz
Check;
Karolina Kalinowska and Marika Gutowska
Formal analysis;
Joanna Orzechowska and Aleksandra Paprocka
Investigation;
Paulina Fijałek, Urszula Świrk and Wiktoria Belcarz
Resources;
Michał Orzechowski
Data curation;
Jan Karczmarz
Writing- rough preparation;
Karolina Kalinowska
Writing- review and editing;
Joanna Orzechowska
Visualization;
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Supervision;
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