Psilocybin-assisted therapy for major depressive disorder: implications for clinical effectiveness, health economics, and regulatory decision-making

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Background: Major depressive disorder (MDD) is a highly prevalent and disabling psychiatric condition associated with substantial clinical, social, and economic burden [1,2]. Despite the availability of conventional antidepressants, their limited effectiveness, delayed onset of action, and high relapse rates have renewed interest in innovative therapeutic approaches [3,4,5]. Psilocybin-assisted therapy (PAT) has emerged as a promising intervention, but its potential integration into national health systems remains uncertain due to regulatory, ethical, and economic constraints [6]. **Objective:** This scoping review aimed to map and critically appraise the available evidence on efficacy and safety of psilocybin for treatment of MDD in otherwise healthy adults, with a particular focus on its relevance for health economic evaluation and regulatory decision-making. **Methods:** A scoping literature review was conducted using PubMed, ClinicalTrials.gov, Cochrane Library, SciELO databases. Clinical trials, systematic reviews, and meta-analyses assessing psilocybin's effects on depressive symptoms in adults diagnosed with MDD were included to comprehensively map existing evidence. Studies addressing secondary depression were excluded from primary analysis. Data extraction focused on study design, population characteristics, intervention protocols, clinical outcomes, safety profiles, and parameters relevant to future pharmacoeconomic modelling. **Results:** Available evidence suggests psilocybin administration is associated with rapid and clinically meaningful reductions in depressive symptoms, with effects observed shortly after treatment and, in some cases, sustained over time. Compared with rapid-acting antidepressants, such as ketamine, psilocybin appears to present lower risk of dependence and fewer toxic adverse effects [7,8]. However, evidence base is limited by small sample sizes, heterogeneous study designs, and scarcity of trials conducted exclusively in patients with primary MDD, restricting robust comparative and economic analyses. **Conclusions:** Psilocybin-assisted therapy represents a potentially transformative intervention for MDD. Nevertheless, current evidence remains insufficient to support definitive conclusions regarding its cost-effectiveness, scalability, and regulatory integration within public health systems. These findings highlight need for multidisciplinary research combining clinical evidence, health economics, regulatory science, and ethical analysis to inform evidence-based policy decisions regarding adoption of psychedelic-assisted therapies.

Palavras-chave: psilocybin; major depressive disorder; depression, psychedelic-assisted therapy

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Referências
[1] Canlı, D; Karaşar, B, Predictors of Major Depressive Disorder: The Need for Social Approval and Self-Esteem. *Alpha Psychiatry* 2021 , *22* ,38-42.
[2] Bitter I; Szekeres G; Cai Q; Feher L; Gimesi-Orszagh J; Kunovszki P, *et al*., Mortality in patients with major depressive disorder: a nationwide population-based cohort study with 11-year follow-up. *Eur Psychiatry* 2024 , *67*.
[3] Cipriani A; Furukawa TA; Salanti G; Chaimani A; Atkinson LZ; Ogawa Y, *et al*., Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Focus (Am Psychiatr Publ)* 2018 , *16* , 420-429.
[4] Gonda X; Tarazi FI; Dome P, The emergence of antidepressant drugs targeting GABAA receptors: a concise review. *Biochem Pharmacol* 2024 , *228*.
[5] Fava GA, May antidepressant drugs worsen the conditions they are supposed to treat? The clinical foundations of the oppositional model of tolerance. *Ther Adv Psychopharmacol* 2020 , *10*.
[6] De Gregorio D; Aguilar-Valles A; Preller KH; Heifets BD; Hibicke M; Mitchell J, *et al*., Hallucinogens in mental health: preclinical and clinical studies on LSD, psilocybin, MDMA, and ketamine. *J Neurosci* 2021 , *41* , 891-900.
[7] Davis AK; Barrett FS; May DG; Cosimano MP; Sepeda ND; Johnson MW, *et al*., Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 2021 , *78* , 481-489.
[8] Johnson MW; Griffiths RR; Hendricks PS; Henningfield JE, The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. *Neuropharmacology* 2018 , *142* , 143-166.