Introduction

Rationale

According to the World Health Organization, around 5% of adults suffer from Major Depressive Disorder (MDD),(1) among whom about a third do not experience adequate remission even after multiple courses of first- or second-generation antidepressants,(2) leading to treatment-resistant depression (TRD). There is no universally agreed-upon definition for TRD. However, the literature most commonly defined TRD as inadequate responses to at least two different antidepressant regimens, despite adequate dosage, duration, and adherence.(3) TRD poses a significant burden on individuals, families, and society, with increased mortality and healthcare costs. According to previous studies, TRD patients had a higher risk of all-cause mortality(4) and higher healthcare costs compared to MDD patients(4, 5).

A lot of efforts have also been made to identify effective medications for TRD. Psilocybin is a substance derived from various mushrooms with fascinating therapeutic properties.(6) Psilocybin acts as an agonist on serotonin (5-hydroxytryptamine) type 2A (5-HT2A) receptors,(7) which may help promote neuroplasticity in cortical neurons and improve depressive symptoms.(8) Large and statistically significant effects (Hedges' g = 1.16 to 1.47) of psilocybin on anxiety and MDD were found in a systematic review of four studies.(9)

No consolidated evidence could be found to show the overall efficacy and safety of psilocybin on TRD treatment. This study aimed to conduct a systematic review and meta-analysis to integrate evidence of psilocybin on TRD and provide evidence of whether psilocybin could be an effective medication for TRD patients.

Objectives

We aim to evaluate the efficacy and safety of psilocybin in improving depressive symptoms in TRD patients and to provide reliable and comprehensive pooled evidence for future reference.

Methods

This systematic review and meta-analysis will adhere to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).(10)

Information sources

Electronic sources including PubMed, Embase, Medline, Cochrane Library, APA PsycINFO, bioRxiv, medRxic, Peer J Preprint, and Clinicaltrials.gov were searched until 14 July 2023. Search terms were: ((Treatment Resistant Depression) OR (Treatment-Resistant Depression) OR (Treatment-Resistant Depressive Disorder) OR (Treatment-Resistant Depressive Disorders) OR (Treatment-Resistant Major Depression) OR (Pharmacotherapy-Resistant Depression) OR (Antidepressant-Resistant Depression)) AND ((psilocybin) OR (psilocybine) OR (psilocibin) OR (psiloc*) OR (psychedelic) OR (COMP360)). No limitation was set for language or year of records.

Study records

Endnote 20 will be used to store all citations of identified records. Full texts will be retrieved for studies with inclusion potential. Two reviewers (QF, JY) will independently screen records and will discuss disagreements to reach a consensus. All included studies will be cross-checked by both researchers (QF, JW) for applicability.

Quality assessment

Risk of bias of included studies will be assessed according to Cochrane Handbook 5.1.(11) Quality of evidence will be evaluated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

approach.(12) Two researchers (QF, JW) will conduct the assessment independently. Any discrepancies will be reviewed by a third researcher (XL) and discussed to reach a final consensus.

Inclusion criteria

- Subjects were identified as TRD patients in original studies;
- Primary intervention was Psilocybin;
- Outcome was related to safety, tolerance, adverse events, or efficacy;
- Randomized control trials (RCTs) or open-label studies.

Exclusion criteria

- Reviews and systematic reviews, observational studies, case studies, and animal studies;
- Post hoc analysis based on published trials;
- Editorials, comments, letters, responses, or guidelines.

Data Extraction

PICO items including, but not limited to, the data source of study, type of study design, demographics and health conditions of the participants, intervention (dose and duration of treatment), outcomes of interest, will be recorded on data extraction form.

Outcome

The primary outcome for efficacy will be the changes in depressive scores. The primary for safety will be the proportion of adverse events (e.g. headache, confusion, suicidal ideation).

Reference

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