INPLASY

CBD for the treatment of positive and negative symptoms in schizophrenia spectrum disorders - A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No financial support.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202460019

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 June 2024 and was last updated on 06 June 2024.

INTRODUCTION

Review question / Objective The purpose of this systematic review and meta-analysis is to evaluate the effectiveness of CBD, both as a monotherapy and as an add-on treatment, in managing symptoms of schizophrenia spectrum disorders.

Rationale The endocannabinoid system has been extensively analyzed throughout the scientific literature due to its associations with schizophrenia spectrum disorders and psychotic symptoms. The use of substances of abuse containing Δ^9-tetrahydrocannabinol, an agonist of the CB1 and CB2 receptors, is recognized as a significant risk factor for the onset of psychotic symptoms or the development of schizophrenia spectrum disorders in individuals with a specific predisposition. However, CBD, another phyto cannabinoid commonly produced by different species of the cannabis genus, has exhibited beneficial effects in certain psychiatric conditions such as anxiety and insomnia. Furthermore, the CB1 receptor has been suggested to have a negative modulating effect on the NMDA receptor, which could potentially contribute to the emergence of psychotic symptoms through a decrease in overall NMDA receptor activity. On the other hand, cannabidiol is recognized for its ability to regulate CB1 receptor activity, resulting in a reduction of its function. These data, taken together, suggest a potential rationale for the use of CBD in the management of patients affected by schizophrenia spectrum disorders. This evidence is supported by clinical trials demonstrating the effectiveness of CBD, both as a standalone treatment and as an adjunct, in reducing the symptoms of schizophrenia, particularly the positive symptoms.

Condition being studied This systematic review with meta-analysis addresses the possible effects of CBD in patients with schizophrenia spectrum disorders. Individuals suffering from one of the conditions included in the spectrum display a wide range of symptomatology, including positive,

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negative, and cognitive symptoms. Positive symptoms include delusions and hallucinations, while negative symptoms include isolation, detachment, and social withdrawal. Cognitive symptoms include dysfunction in concentration, memory, and executive skills. Despite the introduction and common use of antipsychotic drugs, which have shown significant efficacy and impact in managing patients with psychotic spectrum disorders, significant levels of resistance are typically encountered in a clinical setting. Furthermore, antipsychotics commonly used in clinical practice have various side effects, including extrapyramidal symptoms, hyperprolactinemia, metabolic disorders such as type 2 diabetes mellitus and metabolic syndrome, QTc prolongation, and, more rarely, neuroleptic malignant syndrome. These data suggest the need to analyze and evaluate other pharmacological therapeutic approaches for improving the clinical outcomes of these patients.

METHODS

Search strategy We intend to conduct a systematic search in the following databases: Cochrane CENTRAL and PubMed. We will use the following search strategy, adapting it for the Cochrane CENTRAL database

#10 #4 AND #5 AND #9
#9 #6 OR #7 OR #8
#8 marijuana[MeSH Terms]
#7 cannabidiol[MeSH Terms]
#6 ("Cannab*"[Title/Abstract] OR "CBD"[Title/Abstract] OR "hemp"[Title/Abstract] OR "Phytocannab*"[Title/Abstract] OR "Epidyolex"[Title/Abstract] OR "Hashish"[Title/Abstract] OR "Marijuana"[Title/Abstract])
#5 (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh]))
#4 #1 OR #2 OR #3
#3 ((schizo*[Title/Abstract] OR psychotic*[Title/Abstract] OR psychosis[Title/Abstract] OR psychoses[Title/Abstract]))
#2 "Paranoid Disorders"[Mesh]
#1 “Schizophrenia"[Mesh].

Participant or population We will include adults aged 18-65 with a diagnosis of schizophrenia or a related disorder according to the criteria of DSM IV, DSM IV-TR, DSM 5, DSM 5-TR or ICD-10.

Intervention We will include studies that use CBD as monotherapy or added to standard treatment, administered via any route of administration and at any dose. The treatment with CBD should last at least 2 weeks.We will include adults aged 18-65 with a diagnosis of schizophrenia or a related disorder according to the criteria of DSM IV, DSM IV-TR, DSM 5, DSM 5-TR or ICD-10.

Comparator Non-active placebo.

Study designs to be included Randomized clinical trials and crossover studies.

Eligibility criteria
1. Participants with a diagnosis of schizophrenia spectrum disorder.
2. Intervention with CBD, any formulation and route of administration, any dose. The treatment with CBD should last at least 2 weeks.
3. Comparators: non active placebo;
4. Study design: randomized or crossover clinical trials;
5. Reported clinical outcomes: total symptoms, positive symptoms, negative symptoms, anxiety symptoms, depressive symptoms, quality of life.
6. Language: English.

Information sources Electronic databases: PubMed and Cochrane CENTRAL.

Main outcome(s)
1. Changes in total symptoms
2. Changes in positive symptoms
3. Changes in negative symptoms.

Additional outcome(s)
1. Changes in anxiety symptoms
2. Changes in depressive symptoms
3. Changes in quality of life.

Data management The data will be extracted into a relational database by four independent reviewers.

Quality assessment / Risk of bias analysis We will assess the risk of bias using the Risk of Bias 2 tool developed by Cochrane. The assessment will be conducted independently by two separate authors, and any disagreements will be resolved by a third, more experienced author. The assessment will only be carried out for the main outcomes.

Strategy of data synthesis We will use the R-Studio software, specifically the meta package, for data analysis. We will calculate the standardized mean difference for continuous outcomes and the odds ratio and relative risk for binary outcomes. We will also conduct heterogeneity tests and report the values of Q, I^2, and Tau.

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Subgroup analysis We do not aim to produce any subgroup analysis.

Sensitivity analysis We will conduct sensitivity analysis in case of moderate or high heterogeneity detected in the analysis.

Language restriction We will only include articles in English.

Country(ies) involved Italy, Germany.

Keywords Cannabidiol, schizophrenia, positive symptoms, negative symptoms, cognition.

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