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The role of cannabidiol oil in schizophrenia treatment. a systematic review and meta-analysis

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ABSTRACT

The purpose of the present meta-analysis was to assess the efficacy of cannabidiol (CBD) oil in patients with schizophrenia. A search was conducted in EMBASE, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) up to April 24th, 2020. Randomized clinical trials (RCTs), which used CBD oil treatment versus placebo or any other antipsychotic in schizophrenia patients either as monotherapy or add-on therapy, were included. Data were pooled using a random-effects model. The primary outcomes were efficacy as measured by total symptoms of schizophrenia and improvement in cognition. The meta-analysis was registered with PROSPERO [number: CRD42020157146]. Three double-blind RCTs were included. In one study, CBD oil was compared with amisulpride as monotherapy treatment, but no statistically significant difference in overall efficacy was detected between them. No data were available for cognition. The other two studies estimated the effects of CBD oil as add-on treatment compared to placebo; no significant difference was found either in overall efficacy or in cognition. Altogether, insufficient evidence exists on the efficacy and safety of CBD oil in schizophrenia patients. More RCTs, comparing CBD oil with placebo and other antipsychotics are warranted.

1. Introduction

Schizophrenia is one of the most serious mental disorders. It is a chronic condition that presents in early adulthood or late adolescence affecting 0.3–0.7% of all adults, globally (van Os and Kapur, 2009). Pharmacotherapy is the mainstay of schizophrenia treatment (Patel et al., 2014). Both first-generation (typical) antipsychotics (FGAs) and second-generation (atypical) antipsychotics (SGAs) are used as treatment options; however, SGAs are preferred over FGAs because they are associated with fewer side effects such as extrapyramidal symptoms, sedation and sexual dysfunction (Patel et al., 2014). On the other hand, SGAs are associated with a greater risk of weight gain (Patel et al., 2014) and increase in prolactin levels (Picchioni and Murray, 2007).

Nowadays, cannabidiol (CBD) oil products are considered a remedy for many medical conditions and are thus becoming more and more popular, even though they have not been approved, at least yet, by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) or other regulatory authorities. The consumption of non-FDA-approved CBD products has recently raised controversy (Leas et al., 2019; White, 2019). CBD is derived from Cannabis Sativa plants (Adams et al., 1940) and lacks the psychoactive effects of the

Abbreviations: bacs, brief assessment of cognition in schizophrenia; Bprs, brief psychiatric rating scale; Cbd, cannabidiol oil; Central, central register of controlled trials; Cgi, clinical global impressions scale; Ci, confidence interval; Dsm, diagnostic and statistical manual of mental disorders; Embase, excerpta medica database; Fda, food and drug administration; Faah, fatty acid amide hydrolase; Fgas, first-generation (typical) antipsychotics; Gaf, global assessment of functioning scale; ICTRP, WHO International Clinical Trials Registry Platform; MCCB, MATRICS Consensus Cognitive Battery; MD, Mean Difference; PANSS, Positive and Negative Syndrome Scale; PP, Per Protocol; QoL, Quality of life; RCTs, Randomized clinical trials; RR, Risk Ratio

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other major phytocannabinoid Δ9-tetrahydrocannabinol (THC) (Russo, 2011). Unlike Δ9-THC, CBD does not bind to CB1 or CB2 cannabinoid receptors (Thomas et al., 2007); rather it inhibits the degradation of the endogenous cannabinoid anandamide, catalyzed by the enzyme fatty acid amide hydrolase (FAAH), potentially leading to indirect activation of CB1 (De Petrocellis et al., 2011; Elmes et al., 2015). Also, an in vitro study indicated that cannabidiol might act as a partial dopamine D_2 receptor agonist (Bonaccorso et al., 2019), similar to the action of the atypical antipsychotic aripiprazole (Seeman, 2008, 2016) .

The role of CBD in schizophrenia has already been examined in previously published reviews (Bonaccorso et al., 2019; Hoch et al., 2019; Mandolini et al., 2018) and meta-analyses (Black et al., 2019; Whiting et al., 2015), with conflicting results leading to rather unclear and insufficient conclusions. Also, these studies were not strictly focused on CBD but on all different types of medicinal cannabinoids, blurring the picture further. Given the growing interest in the antipsychotic properties of CBD, we aimed to conduct a systematic review and meta-analysis focusing only on RCTs in patients with schizophrenia or other types of schizophrenia-like psychoses that assessed the efficacy of CBD oil compared to placebo or any antipsychotic drug either as monotherapy or add-on therapy.

2. Methods

An a priori written study protocol was published in PROSPERO [number: CRD42020157146] which can be found in Appendix A in the Supplement. The systematic review and meta-analysis was conducted according to PRISMA guidelines (Moher et al., 2009)) (see Appendix B: PRISMA checklist).

2.1. Search strategy and inclusion criteria

We searched EMBASE, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) up to April 24th, 2020 (see Appendix C: Search terms of electronic databases). Furthermore, we searched the literature for previous reviews and inspected the references of all identified studies for more trials. There were no restrictions for language or publication period. We included all relevant randomized controlled trials (RCTs) that compared the effects of CBD oil treatment to placebo or any other antipsychotic as monotherapy or add-on therapy for schizophrenia patients. Two independent reviewers (EK and MS) extracted all data and assessed the trials' quality with the Cochrane Collaboration's risk-of-bias tool (Higgins and Green, 2011). Any disagreement was resolved by a third reviewer (AS). The minimum duration of RCTs was set at 2 weeks (Samara et al., 2015). Participants with schizophrenia and other types of schizophrenia-like psychoses, irrespective of the diagnostic system applied, were included in our meta-analysis. There were no restrictions concerning age, race and gender. We excluded participants with schizophrenia or psychiatric disorders induced by substance abuse.

2.2. Data extraction and outcome variables

All studies were imported into a reference management software Rayyan QCRI (Ouzzani et al., 2016). After duplicate removal, two reviewers (EK, MS) independently inspected all titles and abstracts and obtained the full articles in order to decide whether the studies met the eligibility criteria. Any discordance regarding study eligibility was resolved by a third reviewer (AS). Data from included studies were independently extracted by MS and EK. We have also extracted data presented in graphs and figures. If necessary, in our effort to eliminate missing data and/or ask for clarifications, additional information concerning blinding and allocation concealment was requested by the first or corresponding authors.

Primary outcomes were a) the overall efficacy of cannabidiol oil treatment as measured by rating scales such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Brief Psychiatric Rating Scale (BPRS) (Beller and Overall, 1984) or any other validated scale and b) the assessment of cognition as measured by the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004), the MATRICS Consensus Cognitive Battery (MCCB) Composite Score (August et al., 2012) or any other validated scale.

Secondary outcomes were, clinically important response to treatment, defined as at least 50% reduction of rating scales such as the PANSS or the BPRS, or at least "much improved" on the Clinical Global Impressions Scale (CGI) (Guy, 1976) or as defined by study authors; negative symptoms measured by rating scales such as the PANSS negative subscale, or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989); positive symptoms measured by rating scales such as the PANSS positive subscale; functioning measured by rating scales such as the Global Assessment of Functioning scale (GAF) (Aas, 2010); quality of life (QoL); dropouts due to any cause and due to side-effects; the total number of patients with side-effects; and important individual side-effects such as weight gain, prolactin levels, extrapyramidal symptoms, sedation and sexual side-effects.

2.3. Meta-analytic calculations

Meta-analytic calculations were done with Review Manager 5.3. We employed a random-effects model for analysis. Endpoint values were preferred to change whenever possible since calculation of change needs two assessments (baseline and endpoint) which can be difficult in unstable and difficult-to-measure conditions such as schizophrenia. All analyses were on a per protocol (PP) basis whenever possible. The effect size for dichotomous outcomes was Risk Ratios (RR). The effect size for continuous outcomes was weighted mean difference (MD); if different scales were used, the effect size was calculated as Hedge's adjusted g standardized mean difference (SMD) (Higgins et al., 2019). Effect sizes were presented along with their 95% confidence intervals (CIs). Chi-square and I-squared statistics were considered to investigate statistical heterogeneity between trials. Heterogeneity was tested by inspection of the forest plots with the Chi-square test (significance level a priori set at $p < 0.1$) and the degree of heterogeneity was quantified by the I^2 statistics and its 95% confidence interval (CI).

We have planned several subgroup analyses and meta-regressions. The variables for the subgroup analyses considered a-priori were: a) first episode of schizophrenia, patients with treatment-resistant schizophrenia and other "participant groups", b) acute versus non acute episode of schizophrenia, c) pharmaceutical form of CBD oil (i.e. capsules, oil drops, sprays) and d) sponsored versus non-sponsored trials. The variables for the meta-regression analyses planned a-priori were: a) baseline severity, b) duration of illness, c) duration of the study and d) dosage of CBD oil. Similarly, the following sensitivity analyses on the primary outcomes were planned a-priori: a) grouping of comparator interventions if possible (e.g. antipsychotic group), b) exclusion of studies when randomization was implied, c) exclusion of studies with high risk of bias in blinding and outcome reporting, d) fixed effects instead of random effects model, e) exclusion of Chinese studies and f) exclusion of studies where imputed values were used and inclusion of only the ones that provided SDs.

3. Results

3.1. Description of included studies

From the 3829 studies identified by the search, only 3 double-blind RCTs were included in our meta-analysis. The PRISMA flowchart is shown in Fig. 1 and details of all included studies are presented in Table 1. One double-blind RCT (Leweke et al., 2012) compared CBD with amisulpride [mean daily dose: 757 mg (200–800 mg)] as monotherapy treatment for 4 weeks among patients diagnosed with paranoid

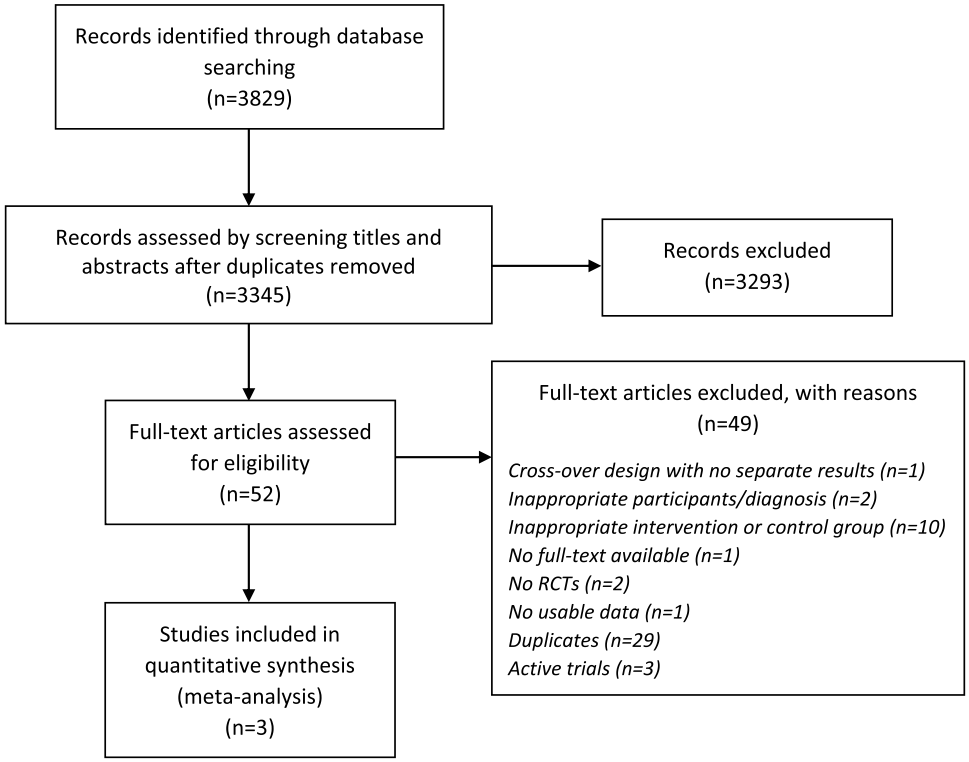

Fig. 1. The PRISMA flowchart
Abbreviations: RCTs= Randomized Controlled Trials.

schizophrenia or schizophreniform psychosis, according to DSM-IV ($N=42$, 30.1 ± 8.9 years old). Two double-blind RCTs (Boggs et al., 2018; McGuire et al., 2018) compared CBD with placebo as an add-on therapy to antipsychotic treatment among patients with schizophrenia or related psychotic disorder as defined by DSM-IV ($N=124$, 42.7 ± 11.4 years old). Participants were treated for a minimum of four weeks on a stable dose of their current antipsychotic medication and then were randomized to 6 weeks treatment with oral cannabidiol [800 mg daily (600–1000 mg)] or placebo.

The baseline symptom severity in the monotherapy study (Leweke et al., 2012) was 93.3 ± 15.7 points in PANSS, whereas in the add-on studies (Boggs et al., 2018; McGuire et al., 2018) it was 79.9 ± 13.8 points, a difference which reached statistical significance ($p<0.0001$, see Supplementary Table D1). The mean participants' age in the add-on studies (Boggs et al., 2018; McGuire et al., 2018) was significantly higher than the one in the monotherapy study (Leweke et al., 2012) ($p<0.0001$, see Supplementary Table D2).

3.2. Risk of bias assessment

Two studies (Leweke et al., 2012; McGuire et al., 2018) reported adequate randomization methods and adequate allocation concealment, whereas one study (Boggs et al., 2018) implied randomization as it was a double-blind study, but the blinding methods were not described. In one study (McGuire et al., 2018) the blinding of participants and personnel was successfully managed (low risk of performance bias) but the risk of bias for blinding of outcome assessment (detection bias) was judged unclear. The other two trials (Boggs et al., 2018; Leweke et al., 2012) had unclear risk of bias for both performance and detection. None of the 3 trials (Boggs et al., 2018; Leweke et al., 2012; McGuire et al., 2018) had addressed incomplete outcome data. Selective reporting was not a source of bias in two studies (Leweke et al., 2012; McGuire et al., 2018) but for the third study the risk was judged unclear (Boggs et al., 2018). All 3 trials (Boggs et al., 2018; Leweke et al., 2012; McGuire et al., 2018) were free from sources of other bias (Supplementary Figures E1 and E2).

3.3. Publication bias

As funnel-plots are based on symmetry, they can only detect publication bias when a reasonable number of studies are available. According to the Cochrane Collaboration's tool, tests for funnel plot asymmetry should not be used when fewer than ten studies are included in the meta-analysis (Egger et al., 1997; Higgins et al., 2019). As we had only 3 studies available, we could not use funnel plots to assess publication bias.

3.4. Comparison: cannabidiol treatment versus amisulpride treatment (monotherapy)

The amisulpride monotherapy study (Leweke et al., 2012) found no difference between CBD oil and amisulpride in the primary outcome, overall efficacy (MD −0.40, 95% CI −14.22 to 13.42, 1 RCT, $N=35$) (Fig. 2). No data were available regarding cognitive assessment. Furthermore, no significant difference was shown in the number of patients responding to treatment, the improvement of positive and negative symptoms or the number of patients withdrawing from treatment (Suppl. Figures F1–6). However, compared with amisulpride, CBD oil was associated with significantly fewer extrapyramidal symptoms (MD −0.22, 95% CI −0.40 to −0.04, 1 RCT, $N=42$) (Suppl. Figure F7), less weight gain (MD −3.40, 95% CI −5,76 to −1.04) (Suppl. Figure F8) and a lower prolactin increase (MD −75.00, 95% CI −109.12 to −40.88) (Suppl. Figure F9). No data were available for the assessment of functioning, quality of life, the total number of patients with side-effects, sedation and sexual side-effects.

3.5. Comparison: cannabidiol treatment versus placebo treatment (add-on therapy)

Regarding overall efficacy of the two studies (Boggs et al., 2018;

Table 1
Characteristics of all included RCTs.

Study	Type of study	Number of participants Mean age (SD)	Primary Outcomes (scale)	Comparator	Treatment duration	Daily dose	Diagnosis
Monotherapy							
Leweke et al. (2012) (published data only)	Parallel, double-blind RCT	N = 42 Age = 40.8 (11.69)	Total psychotic symptoms (PANSS,BPRS)	Amisulpride	4 weeks	200–800 mg	Acute paranoid schizophrenia as defined by DSM-IV
Add-on therapy							
Boggs et al. (2018) (published data only)	Parallel, double-blind RCT	N = 36 Age = 47.4 (9.3)	Total psychotic symptoms (PANSS), Cognition (MATRICS Composite Score)	Placebo	6 weeks	600 mg	Stable chronic DSM IV TR diagnosis of schizophrenia
McGuire et al. (2018) (published data only)	Parallel, double-blind RCT	N = 88 Age = 30.1 (8.9)	Symptom severity (PANSS, SANS), response (CGI-I),cognition (BACS), functioning (GAF) (as key endpoints)	Placebo	6 weeks	1000 mg	Schizophrenia or a related psychotic disorder as defined by DSM-IV

Abbreviations: SD = Standard Deviation, RCT = Randomized clinical trials, PANSS = Positive and Negative Syndrome Scale, BPRS = Brief Psychiatric Rating Scale, SANS = Scale for the Assessment of Negative Symptoms, CGI = Clinical Global Impressions Scale, BACS = Brief Assessment of Cognition in Schizophrenia, GAF = Global Assessment of Functioning scale.

McGuire et al., 2018), augmentation with CBD oil did not show any significant difference compared to placebo (MD −1.07, 95% CI −2.64 to 0.49, 2 RCTs, $N = 122$) (Fig. 3), neither was a significant difference noted with respect to cognition (SMD 0.09, 95% CI −0.27 to 0.45, 2 RCTs, $N = 121$) (Fig. 4).

On the other hand, whereas CBD oil did not significantly improve response to treatment or negative symptoms (Suppl. Figures F10 and F11), it did improve positive symptoms significantly compared to placebo (MD −1.62, 95% CI −2.14 to −1.09, 2RCTs, $N = 122$) (Suppl. Figure F12). No differences were found in terms of functioning, number of patients withdrawing, total number of patients with side-effects and number of patients with individual side-effects such as extrapyramidal effects, weight gain sedation and sexual side-effects (Suppl. Figures F13–21). No data were available for the assessment of quality of life and of prolactin levels.

3.6. Subgroup, meta-regression and sensitivity analyses for the primary outcomes

Subgroup, meta-regression and sensitivity analyses were not undertaken due to insufficient data.

4. Discussion

Over the last two years, there has been increasing media coverage on the alleged benefits of CBD products for a variety of conditions. More and more patients are interested in non-FDA-approved forms of CBD for all types of diseases, including oral CBD oil administration for schizophrenia (White, 2019) despite very limited published evidence supporting a benefit-to-risk ratio regarding its use. Indeed, our meta-analysis was able to identify only three RCTs examining the efficacy of CBD oil as antipsychotic treatment. In our meta-analysis, minimum duration of RCTs was set at 2 weeks. According to Samara et al. (2015), patients who do not show at least a minimal improvement after 2 weeks of antipsychotic treatment, are unlikely to respond or benefit later on.

The monotherapy trial (Leweke et al., 2012), that included patients in acute phase, implied that CBD is as effective as the antipsychotic amisulpride in terms of overall efficacy and number of responders (15/20 responders in CBD group, 14/19 responders in amisulpride group, defined as at least 20% improvement in PANSS total scale), as well as in the number of withdrawals. Furthermore, CBD oil treatment had fewer side-effects such as extrapyramidal symptoms, weight gain and prolactin increase than amisulpride treatment. Later add-on studies (Boggs et al., 2018; McGuire et al., 2018) which were included in this meta-analysis, showed that adding CBD oil to a stable antipsychotic treatment improves positive symptoms significantly compared with placebo, but no differences were found in terms of other efficacy outcomes such as overall efficacy, cognition and negative symptoms. Furthermore, no significant differences were found in terms of safety outcomes such as the number of patients withdrawing, the total number of patients with side-effects and the number of patients with individual side-effects such as sedation, sexual side-effects, extrapyramidal effects or weight gain.

Results between the monotherapy and the add-on CBD oil treatment appear to be conflicting. The monotherapy study (Leweke et al., 2012) implied that CBD oil was not inferior to amisulpride for the treatment of schizophrenia. According to recent studies, amisulpide is one of the most effective atypical antipsychotic drugs for the treatment of schizophrenia (Huhn et al., 2019; Komossa et al., 2010; Leucht et al., 2013, 2009). However, in the add-on studies (Boggs et al., 2018; McGuire et al., 2018), the only significant benefit of CBD oil compared to placebo was the improvement of positive symptoms. Quite a few factors may be responsible for these contradictory results. Firstly, the baseline symptom severity as measured by the PANSS was significantly higher in the monotherapy study (Leweke et al., 2012) than in the add-on studies (Boggs et al., 2018; McGuire et al., 2018). Moreover, the

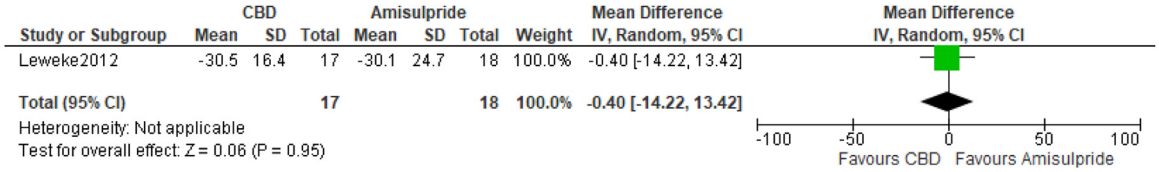

Fig. 2. Forest plot for impact of cannabidiol on total symptoms of schizophrenia (change values measured by PANSS total)
Abbreviations: CBD = Cannabidiol, SD = Standard Deviation, CI = Confidence Interval.

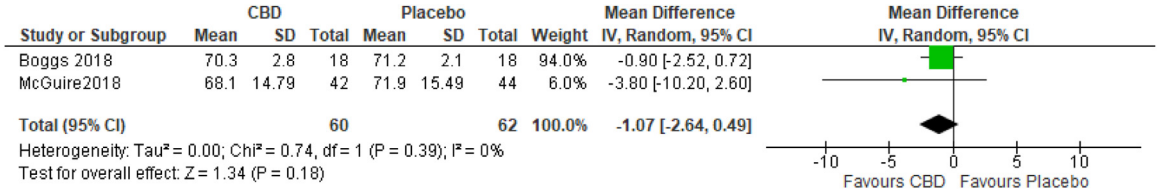

Fig. 3. Forest plot for impact of cannabidiol on total symptoms of schizophrenia (endpoint values measured by PANSS total)
Abbreviations: CBD = Cannabidiol, SD = Standard Deviation, CI = Confidence Interval.

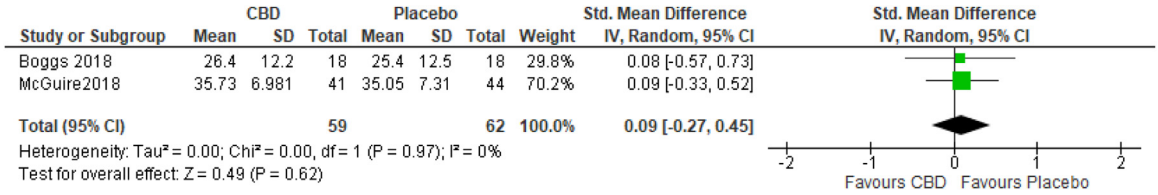

Fig. 4. Forest plot for impact of cannabidiol on cognition (endpoint values measured by MATRICS Composite Score and BACS)
Abbreviations: CBD = Cannabidiol, SD = Standard Deviation, CI = Confidence Interval.

patients in the monotherapy study (Leweke et al., 2012) were suffering from acute schizophrenia, whereas in the add-on studies (Boggs et al., 2018; McGuire et al., 2018) patients were already being treated with a stable dose of antipsychotics for at least 4 weeks before addition of CBD oil, which may have already improved their psychotic symptoms, leaving no room for further improvement. Finally, the mean participants' age in the monotherapy study (Leweke et al., 2012) was significantly lower than in the add-on studies (Boggs et al., 2018; McGuire et al., 2018) which could have affected response to schizophrenia treatment.

Both Black et al. (2019) and Whiting et al. (2015) performed meta-analyses on the impact of CBD on schizophrenia. The results of Black et al. (2019) differ from ours only in terms of positive symptoms when CBD was compared to placebo as add-on therapy since they found no significant difference between interventions. Nevertheless, they used the Hedge's adjusted g SMD instead of MD which attributes different weights to the included studies. Furthermore, both results are not considered robust as they are based on only two studies. In terms of overall efficacy, cognition, negative symptoms and functioning, their results are similar to ours. However, an important difference of our meta-analysis is that, in order to assess the impact of CBD oil on cognition and functioning, Black et al. (2019) analyzed the results of one study (Hallak et al., 2010), which we excluded because a single dose of CBD oil was administered. Moreover, Black et al. (2019) did not estimate the impact of CBD oil in response to treatment and did not examine specific side effects.

The results of the meta-analysis by Whiting et al. (2015) are similar to ours. However, Whiting et al. (2015) did not include add-on studies since these were not published at that time and did not present data in regard to the impact of CBD oil on safety outcomes. Moreover, Whiting et al. (2015) included two monotherapy studies in their analysis, one parallel (Leweke et al., 2012) and one cross-over (Rohleder et al., 2012). The cross-over study (Rohleder et al., 2012) was excluded from our meta-analysis because no separate results from the two arms were presented.

Our meta-analysis has a number of limitations. The most important one is that the findings were based on few participants and a small number of RCTs. Moreover, attrition bias arose in all 3 studies because a per protocol analysis was used. Our response criterion, defined as at least 50% reduction in PANSS and BPRS was not used in any study; instead authors of original studies defined response as at least 20% improvement in PANSS total score. Also, we did not have information on the origin of the CBD oil (i.e., whether the manufacturer of the CBD oil in the 3 studies is different).

Apart from RCTs, non-randomized studies sometimes give tips on how to improve future studies and could be precious for what will be studied in this field in the future. To the best of our knowledge, there are only two observational studies investigating the role of CBD oil in schizophrenia, one case report (Zuardi et al., 1995) and one case series (Zuardi et al., 2006). Initially, Zuardi et al. (1995) found a beneficial effect of CBD oil in reducing psychotic symptoms when added to antipsychotic treatment in a treatment-resistant schizophrenia patient. However, a later study by Zuardi et al. (2006) found mild or no effect of CBD oil monotherapy in the improvement of psychotic symptoms in three treatment-resistant schizophrenia patients (see Appendix G: Table of non-randomized studies).

At present, insufficient evidence exists on the efficacy and safety of CBD oil for patients with schizophrenia. Our analysis suggests that more studies, of longer duration, with larger sample sizes, in different subgroups of schizophrenia patients, comparing CBD oil with more interventions and examining several outcomes should be conducted in order to estimate the role of CBD oil treatment in acute and chronic schizophrenia. Moreover, future trialists should consider examining, not only the clinical outcomes of CBD oil, but also its pharmacokinetics and its relationship to structural and functional cerebral modifications and neurotransmitter signaling. If the administration of CBD oil treatment proves to be effective, ongoing and future studies should also assess the appropriate cannabidiol oil dosage. At the moment, 4 clinical trials are under way trying to answer a wide variety of questions concerning the efficacy and safety of cannabidiol as potential treatment in

schizophrenia (see Appendix H: Table of ongoing trials). The evidence contributing to our meta-analysis is scarce and results can change if further studies become published.

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CRediT authorship contribution statement

Eleftheria Kopelli: Methodology, Formal analysis, Investigation, Data curation, Writing - original draft. **Myrto Samara:** Conceptualization, Methodology, Writing - original draft. **Antonios Siargkas:** Methodology, Formal analysis, Investigation. **Antonis Goulas:** Writing - original draft, Supervision. **Georgios Papazisis:** Formal analysis, Writing - original draft, Supervision. **Michail Chourdakis:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.113246.

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