Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: https://www.tandfonline.com/loi/iemt20

Serious adverse effects of cannabidiol (CBD): a review of randomized controlled trials

Rafael G. dos Santos, Francisco S. Guimarães, José Alexandre S. Crippa, Jaime E. C. Hallak, Giordano Novak Rossi, Juliana Mendes Rocha & Antônio W. Zuardi

To cite this article: Rafael G. dos Santos, Francisco S. Guimarães, José Alexandre S. Crippa, Jaime E. C. Hallak, Giordano Novak Rossi, Juliana Mendes Rocha & Antônio W. Zuardi (2020): Serious adverse effects of cannabidiol (CBD): a review of randomized controlled trials, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1080/17425255.2020.1754793

To link to this article: https://doi.org/10.1080/17425255.2020.1754793

Accepted author version posted online: 09 Apr 2020.

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Opinion on Drug Metabolism & Toxicology*

DOI: 10.1080/17425255.2020.1754793

Review

Serious adverse effects of cannabidiol (CBD): a review of randomized controlled trials

Rafael G. dos Santos[1,2] Francisco S. Guimarães[2,3], José Alexandre S. Crippa[1,2], Jaime E. C. Hallak[1,2], Giordano Novak Rossi[1], Juliana Mendes Rocha[1], Antônio W. Zuardi[1,2,*]

[1] Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil
[2] National Institute of Science and Technology – Translational Medicine, Brazil
[3] Department of Pharmacology, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

***Corresponding author**: Antônio W. Zuardi, Hospital das Clínicas – Terceiro Andar, Av. Bandeirantes, 3900, Ribeirão Preto – São Paulo – Brazil, CEP – 14049-900. Email: awzuardi@fmrp.usp.br

Abstract

Introduction: Recent trials using cannabidiol (CBD) have shown that most acute and prolonged adverse effects of CBD are mild to moderate, with rare serious adverse effects (SAEs). This review focused on analyzing SAEs of CBD and their possible relation to drug-drug interactions.

Areas covered: We systematically analyzed the SAEs reported in randomized controlled trials (RCTs) involving the administration of oral CBD for at least one week in both healthy volunteers and clinical samples.

Expert opinion: SAEs related to CBD in RCT are rare and include mainly elevated transaminases, convulsion, sedation, lethargy, and upper respiratory trait infections. Elevated transaminases are related to concomitant valproate use, while sedation, lethargy, and upper respiratory trait infections are related to concomitant clobazam use. Epileptic patients should be monitored when using CBD concomitantly with these and other antiepileptic drugs for other possible drug-drug interactions

Article highlights

- Cannabidiol (CBD) is a phytocannabinoid devoid of the psychoactive, cognitive and behavioral effects of tetrahydrocannabinol (THC)
- CBD has antipsychotic, anxiolytic, anti-inflammatory, and anticonvulsant properties.
- Recent randomized controlled trials (RCTs) have shown that most acute and prolonged (weeks) adverse effects of CBD are mild to moderate
- Serious adverse effects (SAEs) are rare and include mainly elevated transaminases, convulsion, sedation, lethargy, and upper respiratory trait infections.
- Elevated transaminases are related to concomitant use of CBD with valproate, while sedation, lethargy, and upper respiratory trait infections are related to concomitant clobazam use.
- Epileptic patients should be monitored when using CBD concomitantly with valproate and clobazam and for other possible drug-drug interactions

1. Introduction

Cannabidiol (CBD) is the second most abundant phytocannabinoid in the psychoactive cannabis varieties, while it is the main compound in non-psychoactive hemp varieties (1). CBD does not induce the typical euphoriant and pleasurable effects of cannabis, which are produced by tetrahydrocannabinol (THC), the compound also responsible for the dependence potential and negative effects of prolonged cannabis use (2). Moreover, there is evidence that CBD has opposite behavioral, subjective and cognitive effects compared to THC, and may also counteract its effects (3-5).

The different profile of behavioral, subjective and cognitive effects of CBD compared to THC is also reflected in their mechanisms of action. THC is a partial agonist of cannabinoid receptors type-1 and type-2 ($CB_{1/2}$). These receptors, together with their endogenous ligands (endocannabinoids) anandamide (AEA) and 2-arachidonyl glycerol (2-AG) and the respective synthesis and degradation enzymes (fatty acid amide hydrolase [FAAH] and monoacyglycerol lipase [MAGL]) form the endocannabinoid system (ECS) (6,7). CBD, on the contrary, does not display high affinity for $CB_{1/2}$ and seems to act as a negative allosteric modulator of CB_1 receptors and an antagonist of CB_2 receptor. Moreover, CBD may also inhibit AEA hydrolysis, act as an antagonist at the putative novel cannabinoid receptor G protein-coupled receptor 55 (GPR55), and as an agonist at the transient receptor potential vanilloid 1 and 2 receptor channels ($TRPV_{1/2}$) and the serotonergic 5-HT_{1A} receptors, among others mechanisms (8,9).

In the last 40 years, evidence from preclinical and clinical studies (including a growing number of randomized controlled trials (RCTs)) has accumulated reporting therapeutic effects of CBD on several neurological and psychiatric disorders, including epilepsy (10-13), Parkinson's disease (14), psychosis (15-18) and anxiety (16,18), among others. Moreover, CBD is also being studied in some systemic diseases in RCTs (Jadoon et al, 2016; Naftali et al. 2017).

Evidence from previous reviews on the safety of CBD (19,20) and from the above cited RCTs suggest that, overall, CBD has a favorable safety profile. The most common adverse effects observed in RCTs include mild to moderate gastrointestinal (diarrhea, nausea, vomiting), central (sedation, somnolence, fatigue, convulsion), and metabolic (increases in serum aminotransferases, decreased appetite) effects, which are mainly reported in studies with epileptic patients (10-13). Studies in epilepsy also show that the overall occurrence of adverse effects, treatment discontinuation, and study withdrawals due to adverse effects are higher in the CBD treatment groups when compared to placebo (10-13).

A possible explanation for the higher reporting of adverse effects in the studies of CBD and epilepsy involves drug-drug interactions, especially with drugs widely used in the treatment of severe forms of epilepsy (such as Dravet and Lennox-Gastaut syndromes), including clobazam and valproic acid/valproate (21,22). Second-line drugs typically include stiripentol, topiramate and levetiracetam, which may also cause drug-drug interactions with concomitant CBD use (21-24). Most of these interactions could be explained by inhibition of the catalytic activity of the cytochrome P450 (CYP) 2C19 and 3A4 enzymes induced by CBD (21-24).

Although previous reviews have reported the overall safety of CBD and the adverse effects observed in RCTs, to the best of our knowledge there is no review focused on the serious adverse effects (SAEs) associated with CBD use. Thus, the objective of the present review is to systematically assess the occurrence of SAEs reported in RCTs of prolonged (at least one week) administration of CBD. We will assess the possible association of these SAEs with drug-drug interactions.

2. Method

In this review, a systematic analysis of existing literature regarding the safety of long-term (at least one week) oral CBD administration in humans has been compiled. A PubMed search using the terms (cannabidiol) AND (randomized clinical trial OR double-blind OR placebo controlled) was performed until March 2020. We also reviewed 25 selected systematic reviews and/or meta-analysis published in the last six years (2014-2020) that analyzed clinical trials assessing the therapeutic potential of cannabinoids in general (25-28) and specifically for neurological disorders (mostly epilepsy) (10-13,29,30), psychiatric/mental disorders (15-18,30,32-34), and chronic pain (related or not to psychiatric and neuropsychiatric disorders) (35-41).

Inclusion criteria consisted of: (a) randomized, double-blind, placebo- and active comparator-controlled trials with at least two treatment arms; (b) trials published as full-texts in peer-reviewed journals; (c) studies involving the oral administration of pure CBD or standardized CBD extracts with <3% THC; (d) studies with duration of at least one week; and (e) studies with healthy volunteers and clinical populations. Exclusion criteria consisted of: (a) observational studies; (b) review articles; (c) case series/reports; (d) letters to the editor; and (e) conference abstracts. The process was conducted independently by three reviewers independently (GNR, JMR, RGS). In cases of disagreement, the reviewers discussed their reasons for inclusion or exclusion and if a consensus was not reached, a fourth author (AWZ) was consulted to decide for the inclusion or exclusion of the article. The following data were extracted: authors and year of publication; study design; participants characteristics; CBD product information/dosage; adverse effects and SAEs. We had a particular interest in identifying SAEs, which the regulatory drug agencies consider when the patient outcome is death, life-threatening, require hospitalization, require intervention to prevent damage, or cause disability. In the present review, SAEs were identified if the studies' authors considered that they fulfilled one of these characteristics or if they led to study withdrawal.

3. Results and discussion

3.1. Summary of results

We found 18 RCTs involving a total of 1127 subjects, with duration ranging from one to 18 weeks, and CBD daily dose ranged from 20 to 1500 mg/day. Only one study was a crossover trial, all other trials were parallel-arm studies. Four double blind RCTs (41-44) involved the administration of CBD to healthy volunteers (n=87; CBD n=48, placebo n=39), with duration ranging from one to four weeks, CBD daily dose ranging from 210 to 1500 mg/day. No study had concomitant medications. Six RCTs (42,46-50) involved the administration of CBD to epileptic patients (n=763; CBD n=464, placebo n=299), with duration ranging from three to 18 weeks, CBD daily dose ranging from 200 to 1400 mg/day. All RCTs were add-on studies with concomitant use of antiepileptic drugs. The most frequently antiepileptic drugs administered together with CBD were clobazam, valproate, levetiracetam, and topiramate.

Eight RCTs (51-58) involved the administration of CBD to other clinical populations (n=282; CBD n=143, placebo n=139), with duration ranging from four to 13 weeks, and CBD daily dose ranging from 20 to 1000 mg/day. Three of these RCTs (52,54,55) assessed the effects of CBD in psychotic patients (n=163; CBD n=81, placebo n=63; positive comparator [amisulpride] n=19), with duration ranging from four to six weeks. CBD daily dose ranged from 600 to 1000 mg/day and, with the exception of the study using the positive comparator, the others were add-on studies with concomitant use of multiple antipsychotics and other drugs. The other five RCTs (51,53,56-58) involved the administration of CBD in Huntington's disease, Parkinson's disease (add-on), type 2 diabetes (add-on), Crohn's disease (add-on), and social anxiety disorder (SAD) (one RCT for each clinical indication) (see Supplementary Material for detailed information on each RCT).

CBD showed moderate/mild adverse effects in most studies. Common adverse effects included somnolence, sedation, fatigue, dizziness, headache, diarrhea, nausea, decreased appetite,

abdominal discomfort/pain, vomiting and rash. In addition to these effects, other adverse effects were more commonly or only reported in the RCTs involving epileptic patients: elevated transaminases, pyrexia, upper respiratory tract infection, and convulsion (see Supplementary Material for detailed information on each RCT).

3.2. Serious adverse effects related to cannabidiol

SAEs were reported in seven RCTs (46-50,54,55): five trials on epilepsy (all epilepsy trials) and two trials on psychosis. No serious adverse effects were observed in the RCTs involving healthy volunteers. A summary of the results for the 18 RCTs is shown on Tables 1–3.

The SAEs reported in the psychosis trials were sedation (one patient; 54) and gastrointestinal disorder (one patient; 55). In one trial (54), mild sedation was more prevalent in the CBD group (20%) compared to the placebo group (5%), and although this patient withdrew from the study due to sedation this occurred in the initial phase of the treatment (before the 2nd week of the study) and was not classified as a SAE by the authors (we included as SAE due to patient withdrawal). Sedation is a common effect of CBD, and although some drug-drug interactions could be responsible for the increased sedation in this patient, it seems more likely that this was a direct effect of CBD. Moreover, patients in this trial were using multiple drugs from different classes (antipsychotics, antidepressants, anticholinergic, anticonvulsants/mood stabilizers, and benzodiazepines), which makes it difficult to attribute possible interactions with CBD to individual drugs. A similar case seems have also been reported (55), which reports increased gastrointestinal symptoms (nausea, diarrhea, abdominal pain, and vomiting) in eight patients in the CBD group compared to three in the placebo group. These effects caused the withdrawal of one patient, but no SAEs were reported by the authors in the CBD group (it was considered here as SAE due to patient withdrawal). It is also possible that these gastrointestinal symptoms could be causes by the excipients in the CBD formulation (usually some kind of oil), but no information on CBD's formulation was given in any of the CBD/psychosis trials. A summary of the results for the two RCTs involving CBD administration to patients with psychosis is shown on Table 3.

Regarding the five RCTs in epilepsy, all of them reported the total number of SAE, but the number of each SAE is not clearly stated. Thus, the SAEs reported by the studies' authors are described without quantitative analysis. The most common SAEs were elevated transaminases (46-49), convulsions (46,47,49,50), rash (48,49), elevated γ-glutamyltransferase (48,49), lethargy (48,49), somnolence (48), and pneumonia (49). In addition, respiratory failure, diarrhea, vomiting, viral infection, increased concentration of antiepileptic drugs, restlessness, hypercapnia, and hypoxia were reported in one of the RCTs (49). Constipation and worsening of chronic cholecystitis were reported in another (48), while pyrexia was reported in another trial (47). One trial (50) did not describe any observed SAEs. Only one death occurred due to respiratory failure (49).

One trial did not observe serious adverse effects (42). This could be related to the lower dose of CBD used (200–300 mg/day), or to the absence of some antiepileptic drugs present in the other RTS, such as clobazam and valproate. As will be discussed below, these two drugs seem to be involved in the main SAEs observed in the epilepsy trials: risk of hepatic toxicity due to elevated transaminases (and maybe γ-glutamyltransferase) in the case of valproate, and somnolence, lethargy, pneumonia, and respiratory failure in the case of clobazam. A summary of the results for the five RCTs involving CBD administration to patients with epilepsy is shown on Table 2.

Figures 1 and 2 show that the SAEs were more prevalent in studies with resistant epileptic patients and with the concomitant use of antiepileptic drugs. Studies with samples of healthy subjects or with other disorders and use of non-antiepileptic drugs did not show SAEs with the exception of two patients with schizophrenia who withdraw from the study, although the authors did not consider these events as SAEs. These observations suggest an association between SAEs and concomitant use of CBD and antiepileptic drugs.

3.3. Valproate and the risk of drug-induced liver injury (DILI)

The most common SAEs in the epilepsy RCTs was elevated transaminases (alanine aminotransferase or aspartate aminotransferase levels >3 times the upper limit of the normal range), which caused the withdrawal or treatment discontinuation of at least 15 patients in all trials combined. Most of these patients (all in some trials) were using valproate, suggesting a drug-drug interaction in which CBD could be potentiating a valproic acid–induced change in hepatic aminotransferase levels (and possibly in γ-glutamyltransferase levels). The hypothesis of a CBD interference in the metabolism of valproate could be suggested since a secondary metabolism route of this drug (responsible for around 10%) involves CYP2C9, which is inhibited by CBD (59). However, there is clinical evidence that CBD had no effect on systemic levels of valproate (24,47,60), which suggests other pharmacokinetic or a pharmacodynamic interaction. Previous studies showed that both CBD and valproate are highly bound to plasma proteins (59,61). Although there is no direct clinical evidence of this interaction, we can infer that a possible interference in this protein binding could result in elevation of the free and available portions of the drug. Future trials should assess this possibility directly.
Importantly, no cases of DILI were reported, since bilirubin levels did not reach >2 times the upper limit of the normal range and most cases resolved while the patients continued taking CBD, suggesting a transient metabolic stress on the liver. Thus, although there seems to be limited risk of CBD-induce DILI, patients using CBD and valproate should have their liver enzymes constantly monitored.

3.4. Clobazam and the risk of somnolence, lethargy, pneumonia, and respiratory failure

The most investigated pharmacokinetic interaction between CBD and an antiepileptic drug involves its association with clobazam and its metabolite, N-desmethylclobazam (21-24,47). Increases in N-desmethylclobazam plasma levels have been directly observed previously in humans (21,23) and were also observed in one of the selected trials (47).
The interaction between CBD and clobazam seems to include both pharmacodynamic and pharmacokinetic mechanisms. Preclinical evidence shows that CBD can inhibit the catalytic activity of the cytochrome P450 (CYP) 2C19, which causes a significant increase in plasma concentrations of N-desmethylclobazam in humans (21,23,47). Further, clobazam may inhibit CYP2D6 and increase the levels of the CBD active metabolite 7-hydroxy-CBD, and CBD and clobazam together could enhance GABAergic neurotransmission (22,24), although direct evidence for these interactions is lacking.
Both CBD and clobazam can cause sedation and somnolence, and clobazam alone may also cause lethargy, pneumonia, and respiratory failure (FDA, 2016). Indeed, there is direct evidence that concomitant use of clobazam with opioids and other central nervous system depressants may result in profound sedation, respiratory depression, coma, and death (FDA, 2016). Thus, concomitant use of CBD and clobazam could be related not only to a possible increase in efficacy, but also to increased toxicity.
In one study (48), three patients in the CBD group had pneumonia alone (two were using clobazam), two patients had pneumonia and acute respiratory failure (both using clobazam), one patient had respiratory failure alone (using clobazam), and one patient died due to respiratory failure (not clear if was using clobazam). Thus, in the five cases of pneumonia in the CBD group, four patients were concomitantly using clobazam. Regarding the four cases of

respiratory failure, three were using CBD concomitantly using clobazam, and in the other case this was not clear.
All events were considered unrelated to CBD by the authors, which suggests that these effects could be related to increased plasma levels of N-desmethylclobazam, and thus, increased toxicity. In another trial (50), although the authors did not give detailed information on the SAEs observed in the trial, pneumonia was reported in 10 patients. Therefore, patients using CBD and clobazam should be carefully monitored for increases sedation, somnolence, lethargy, pneumonia and respiratory failure.

3.5. Cannabidiol and other serious adverse effects
Other serious adverse effects observed in the epilepsy RCTs included convulsions (46,47,49,50), rash (47,49), diarrhea, vomiting, viral infection, increased concentration of antiepileptic drugs, restlessness, hypercapnia, and hypoxia (49), constipation and worsening of chronic cholecystitis (48), and pyrexia (47). It is possible that some of these effects could be related to CBD, other antiepileptic drugs, or drug-drug interactions. Indeed, besides inhibition of the cytochrome P450 enzymes CYP2C19 and 3A4, in vitro studies show that CBD may inhibit the activity of other CYPs (CYP1A1, 1A2, 1B1, 2B6, 2C6, 2C8, 2C9, 2J2, 3A5, and 3A7), uridine 5'-diphospho (UDP)-glucuronosyltransferase (UGT) enzymes (UGT1A9 and UGT2B7), and esterases (carboxylesterase 1, CES1) (24).
However, although one study reported increases in the levels of topiramate, rufinamide, zonisamide and eslicarbazepine when used concomitantly with CBD, these increases did not exceed the therapeutic range of these drugs (23). Further, another study reported that plasma levels of valproate, levetiracetam, topiramate, and stiripentol were not affected by CBD (47). Therefore, it is not clear which of the observed SAEs are directly related to increased concentration of antiepileptic drugs or other types of drug-drug interactions.
In the case of convulsions (including status epilepticus), it should be considered that the RCTs involve patients with serious and sometimes devastating epileptic syndromes that are often resistant to treatment. Therefore, the occurrence of convulsions in these trials could also reflect the complex clinical characteristics of the sample and/or a lack of efficacy rather than a direct effect of CBD or other antiepileptic drugs. Nonetheless, an impairment of epilepsy control is a potential side effect for CBD and other anticonvulsant drugs and has been considered so by several of the reviewed studies. Moreover, the plasmatic therapeutic window of CBD in epilepsy and other disorders is not clearly defined. Clinically used anticonvulsants such as phenytoin, for example, can impair epilepsy control at higher plasma concentrations.
Rash has been observed in RCTs involving CBD administration to healthy volunteers (44), but not in other clinical samples not involving epilepsy (see Table 1 and 3). Thus, it is possible that rash could be caused by CBD. Nevertheless, other antiepileptic drugs, including clobazam, may also cause rash. Even so, the incidence of rash in one study (50) was higher in patients using CBD with clobazam (n=9) than in patients without clobazam (n=1). However, considering that rash was reported as a SAE in two of the epilepsy RCTs (48,49) and was associated with withdrawal of patients, subjects taking CBD alone or concomitant with other antiepileptic drugs (especially clobazam) for prolonged periods of time should be monitored for rash and have dose reduction/adjustment or treatment discontinuation.
Diarrhea and vomiting were observed in healthy volunteers (43-45) and psychotic patients (55), but not in other samples (see Table 1 and 3). Therefore, these reactions seem to be directly related to CBD, although the possibility of drug-drug interactions (including with clobazam, which can increase vomiting) should not be excluded.
Viral infection, hypercapnia, restlessness, and hypoxia were not observed in healthy volunteers or other samples (see Table 1 and 3), being observed in only one study (49). Considering that this trial reported pneumonia and respiratory failure in some patients and that these effects could be related to a CBD-clobazam interaction, these other SAEs could represent a continuum of effects related to decreased immunological function and increased susceptibility to upper

respiratory tract infections caused by clobazam. Pyrexia (47,50) could also be related to these symptoms.
Constipation and worsening of chronic cholecystitis (48) could reflect gastrointestinal reactions to CBD, since abdominal discomfort/pain was observed in healthy volunteers (43-45) and psychotic patients (55). Indeed, in the psychosis trial one patient withdrew from the CBD group due to nausea, diarrhea, abdominal pain, and vomiting. Nevertheless, drug-drug interactions should not be excluded as possible explanations for these symptoms.
Finally, it is also important to consider the vehicle of CBD preparations (e.g., sesame oil, corn oil, olive oil, excipients), which could also work in parallel with antiepileptic drugs to induce possible drug-drug interactions (23).

4. Expert opinion

The medical use of CBD and other cannabinoids is increasing, but this is not followed by a similar increase in controlled studies assessing safety and efficacy. Most RCTs, systematic reviews and meta-analysis show that the adverse effects of products containing CBD are generally mild-to-moderate, with rare cases of SAEs leading to study withdrawal. These observations are in line with the findings of the present review, where we systematically analyzed all RCTs (n=18) involving the administration of CBD for at least one week to both healthy volunteers and clinical samples.
No SAEs were observed in the studies with healthy volunteers, which corroborates previous studies and reviews. No such effects were observed in patients with Huntington's disease, Parkinson's disease, type 2 diabetes, Crohn's disease, and social anxiety disorder, even considering that in some of these studies patients were taking other medications.
In the case of the studies with psychosis, the observed effects (sedation and gastrointestinal discomfort) led to study withdrawal of two patients and could be attributed to CBD since both effects have been observed in studies with healthy volunteers. However, drug-drug interaction should not be excluded as a possible explanation, especially in relation to sedation, observed with several antipsychotics.
The higher incidence of SAEs was observed in the RCTs with epilepsy. Severe somnolence, lethargy, increases in hepatic transaminases, rash, and pneumonia accompanied or not with respiratory failure are some of the most relevant effects observed. Importantly, these effects seem to be related to drug-drug interactions, especially with valproate in the case of increases in hepatic transaminases and with clobazam in the case of somnolence, lethargy, rash, and pneumonia accompanied with respiratory failure.
It is still unclear if the exact mechanism of the interaction between CBD and valproate is associated with some pharmacokinetic or pharmacodynamic interaction between the two drugs. However, the fact that most hepatic transaminase changes observed have occurred with this association suggests caution. Importantly, it must also be considered that elevated transaminase is a symptom of liver damage, not the proximal cause. Therefore, more clinical studies are needed to elucidate this association. The mechanisms of interaction between CBD and clobazam are better known, involving the inhibition of cytochromes P450 and elevated plasma levels of these compounds and their metabolites. Moreover, a pharmacodynamic interaction could occur since CBD and clobazam enhance GABAergic neurotransmission.
Several of these events led to patient withdrawal, although they occurred in a minority of patients (~20 patients in the five RCTs). However, considering their morbidity and the already delicate health of many of the epileptic patients, researchers and health professionals should monitor epileptic patients using CBD concomitant with valproate and clobazam, with attention in the plasma level of drugs and symptoms of the patients. Patients using clobazam should be especially careful when they experience somnolence or lethargy, which usually precede more severe conditions such as pneumonia and respiratory failure.
Regarding other medications, more studies are necessary to investigate their possible interactions with CBD and other cannabinoids. This is especially relevant in the case of

antiepileptic drugs, since preclinical and preliminary human studies have reported evidence of pharmacokinetic and/or pharmacodynamic interactions with CBD.

Funding
This paper was not funded

Declaration of interest
RGS is Fellow of the Programa Nacional de Pós-Doutorado, Brazil (PNPD/CAPES). FSG, JAC, JEH and AWZ and are recipients of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) 1A productivity fellowships. Research was supported in part by grants from (i) Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP); (ii) Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); (iii) Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES); (iv) Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FAEPA, Brazil); (v) Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, São Paulo, Brazil (USP-SP); and (vi) National Institute for Translational Medicine (INCT-TM; CNPq/FAPESP, Brazil). GNR received funding from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil). JMR received funding from FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo, Brazil).
FSG, JAC, JH and AWZ are co-inventors (Mechoulam R, Crippa JA, Guimaraes FS, Zuardi A, Hallak, JE, Breuer A) of the patent “Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023” Def. US no. Reg. 62193296; 29/07/2015; INPI on 19/08/2015 (BR1120150164927). The University of São Paulo has licensed the patent to Phytecs Pharm (USP Resolution No. 15.1.130002.1.1). The University of São Paulo has an agreement with Prati-Donaduzzi (Toledo, Brazil) to “develop a pharmaceutical product containing synthetic cannabidiol and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson's disease, and anxiety disorders.” JAC and JEH have received travel support from and are medical advisors of BSPG-Pharm. JAC has a grant from University Global Partnership Network (UGPN)—Global priorities in cannabinoid research excellence. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

References are highlighted as being '*' – of interest, or "" – of considerable interest.**

1. Clark RC, Merlin DM. Cannabis: evolution and ethnobotany. Berkeley (CA): University of California Press, 2013.
2. Volkow ND, Swanson JM, Evins AE, et al. Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. JAMA Psychiatry. 2016 Mar;73(3):292-7.
3. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 2010 Feb;35(3):764-74.
4. Martin-Santos R, Crippa JA, Batalla A, et al. Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Curr Pharm Des. 2012;18(32):4966-79.
5. Zuardi AW, Shirakawa I, Finkelfarb E, et al. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology. 1982;76(3):245-50.
6. Maccarrone M, Bab I, Biro T, et al. Endocannabinoid signaling at the periphery: 50 years after THC. Trends Pharmacol Sci. 2015 May;36(5):277-96.
7. Maccarrone M, Guzman M, Mackie K, et al. Programming of neural cells by (endo)cannabinoids: from physiological rules to emerging therapies. Nat Rev Neurosci. 2014 Dec;15(12):786-801.
8. Campos AC, Fogaca MV, Scarante FF, et al. Plastic and Neuroprotective Mechanisms Involved in the Therapeutic Effects of Cannabidiol in Psychiatric Disorders. Front Pharmacol. 2017;8:269.
9. Dos Santos RG, Hallak JEC, Crippa JAS. Neuropharmacological effects of the main phytocannabinoids: a narrative review. In: Monti J, Murillo-Rodriguez E, Pandi-Perumal SR (eds.). Cannabinoids and neuropsychiatric disorders. Switzerland: Springer Nature, 2020.
10. de Carvalho Reis R, Almeida KJ, da Silva Lopes L, et al. Efficacy and adverse event profile of cannabidiol and medicinal cannabis for treatment-resistant epilepsy: Systematic review and meta-analysis. Epilepsy Behav. 2020 Jan;102:106635.***Systematic review and meta-analysis of randomized trials of cannabidiol and medicinal cannabis for treatment-resistant epilepsy.***
11. Elliott J, DeJean D, Clifford T, et al. Cannabis-based products for pediatric epilepsy: A systematic review. Epilepsia. 2019 Jan;60(1):6-19.
12. Lattanzi S, Brigo F, Trinka E, et al. Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. Drugs. 2018 Nov;78(17):1791-1804.***Systematic review and meta-analysis of randomized trials of cannabidiol for treatment-resistant epilepsy.***
13. Lattanzi S, Brigo F, Trinka E, et al. Adjunctive Cannabidiol in Patients with Dravet Syndrome: A Systematic Review and Meta-Analysis of Efficacy and Safety. CNS Drugs. 2020 Mar;34(3):229-241.***Systematic review and meta-analysis of randomized trials of cannabidiol for treatment-resistant epilepsy.***
14. Crippa JAS, Hallak JEC, Zuardi AW, et al. Is cannabidiol the ideal drug to treat non-motor Parkinson's disease symptoms? Eur Arch Psychiatry Clin Neurosci. 2019 Feb;269(1):121-133

15. Batalla A, Janssen H, Gangadin SS, et al. The Potential of Cannabidiol as a Treatment for Psychosis and Addiction: Who Benefits Most? A Systematic Review. J Clin Med. 2019 Jul 19;8(7).

16. Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry. 2019 Dec;6(12):995-1010.
17. Davies C, Bhattacharyya S. Cannabidiol as a potential treatment for psychosis. Ther Adv Psychopharmacol. 2019;9:2045125319881916.
18. Hoch E, Niemann D, von Keller R, et al. How effective and safe is medical cannabis as a treatment of mental disorders? A systematic review. Eur Arch Psychiatry Clin Neurosci. 2019 Feb;269(1):87-105.
19. Bergamaschi MM, Queiroz RH, Zuardi AW, et al. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf. 2011 Sep 1;6(4):237-49.
20. Iffland K, Grotenhermen F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis Cannabinoid Res. 2017;2(1):139-154.***Important review on the safety of cannabidiol in humans.***
21. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015 Aug;56(8):1246-51.****Important study on the concomitant use of cannabidiol and clobazam in humans.***
22. Miziak B, Walczak A, Szponar J, et al. Drug-drug interactions between antiepileptics and cannabinoids. Expert Opin Drug Metab Toxicol. 2019 May;15(5):407-415.
23. Gaston TE, Bebin EM, Cutter GR, et al. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia. 2017 Sep;58(9):1586-1592.****Important study on the concomitant use of cannabidiol and antiepileptic drugs in humans.***
24. Qian Y, Gurley BJ, Markowitz JS. The Potential for Pharmacokinetic Interactions Between Cannabis Products and Conventional Medications. J Clin Psychopharmacol. 2019 Sep/Oct;39(5):462-471.
25. Lim K, See YM, Lee J. A Systematic Review of the Effectiveness of Medical Cannabis for Psychiatric, Movement and Neurodegenerative Disorders. Clin Psychopharmacol Neurosci. 2017 Nov 30;15(4):301-312.
26. Pratt M, Stevens A, Thuku M, et al. Benefits and harms of medical cannabis: a scoping review of systematic reviews. Syst Rev. 2019 Dec 10;8(1):320.
27. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. Jama. 2015 Jun 23-30;313(24):2456-73.
28. Wong SS, Wilens TE. Medical Cannabinoids in Children and Adolescents: A Systematic Review. Pediatrics. 2017 Nov;140(5).

29. Koppel BS, Brust JC, Fife T, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014 Apr 29;82(17):1556-63.
30. Stockings E, Zagic D, Campbell G, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. J Neurol Neurosurg Psychiatry. 2018 Jul;89(7):741-753.
31. Hindocha C, Cousijn J, Rall M, et al. The Effectiveness of Cannabinoids in the Treatment of Posttraumatic Stress Disorder (PTSD): A Systematic Review. J Dual Diagn. 2020 Jan-Mar;16(1):120-139.
32. Orsolini L, Chiappini S, Volpe U, et al. Use of Medicinal Cannabis and Synthetic Cannabinoids in Post-Traumatic Stress Disorder (PTSD): A Systematic Review. Medicina (Kaunas). 2019 Aug 23;55(9).
33. Sarris J, Sinclair J, Karamacoska D, et al. Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. BMC Psychiatry. 2020 Jan 16;20(1):24.
34. Wilkinson ST, Radhakrishnan R, D'Souza DC. A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications. J Clin Psychiatry. 2016 Aug;77(8):1050-64.

35. Aviram J, Samuelly-Leichtag G. Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pain Physician. 2017 Sep;20(6):E755-e796.
36. Häuser W, Fitzcharles MA, Radbruch L, Petzke F. Cannabinoids in pain management and Palliative medicine: an overview of systematic reviews and prospective observational studies. Dtsch Arztebl Int 2017; 114: 627–34.
37. Hauser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - An overview of systematic reviews. Eur J Pain. 2018 Mar;22(3):455-470.
38. Hauser W, Welsch P, Klose P, et al. Efficacy, tolerability and safety of cannabis-based medicines for cancer pain : A systematic review with meta-analysis of randomised controlled trials. Schmerz. 2019 Oct;33(5):424-436.
39. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. Jama. 2015 Jun 23-30;313(24):2474-83.
40. Mucke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018 Mar 7;3:Cd012182.
41. Rabgay K, Waranuch N, Chaiyakunapruk N, et al. The effects of cannabis, cannabinoids, and their administration routes on pain control efficacy and safety: A systematic review and network meta-analysis. J Am Pharm Assoc (2003). 2020 Jan - Feb;60(1):225-234.e6.
42. Cunha JM, Carlini EA, Pereira AE, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology. 1980;21(3):175-85.
43. Taylor L, Gidal B, Blakey G, et al. A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. CNS Drugs. 2018 Nov;32(11):1053-1067.
44. Taylor L, Crockett J, Tayo B, et al. Abrupt withdrawal of cannabidiol (CBD): A randomized trial. Epilepsy Behav. 2020 Mar;104(Pt A):106938.
45. Sultan SR, O'Sullivan SE, England TJ. The effects of acute and sustained cannabidiol dosing for seven days on the haemodynamics in healthy men: A randomised controlled trial. Br J Clin Pharmacol. 2020 Mar 3.
46. Devinsky O, Cross JH, Wright S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017 Aug 17;377(7):699-700.***Important trial of cannabidiol and epilepsy.***
47. Devinsky O, Patel AD, Thiele EA, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology. 2018 Apr 3;90(14):e1204-e1211.***Important trial of cannabidiol and epilepsy.***
48. Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. New England Journal of Medicine. 2018;378(20):1888-1897.***Important trial of cannabidiol and epilepsy.***
49. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018 Mar 17;391(10125):1085-1096.***Important trial of cannabidiol and epilepsy.***
50. Miller I, Scheffer IE, Gunning B, et al. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA Neurol. 2020 Mar 2.***Important trial of cannabidiol and epilepsy.***
51. Consroe P, Laguna J, Allender J, et al. Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem Behav. 1991 Nov;40(3):701-8.
52. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry. 2012 Mar 20;2(3):e94.***Important trial of cannabidiol and psychosis.***

53. Chagas MH, Zuardi AW, Tumas V, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacol. 2014 Nov;28(11):1088-98.***Important trial of cannabidiol and Parkinson's disease.***
54. Boggs DL, Surti T, Gupta A, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology. 2018 Jul;235(7):1923-1932.***Important trial of cannabidiol and psychosis.***
55. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial. Am J Psychiatry. 2018 Mar 1;175(3):225-231.***Important trial of cannabidiol and psychosis.***
56. Jadoon KA, Ratcliffe SH, Barrett DA, et al. Efficacy and Safety of Cannabidiol and Tetrahydrocannabivarin on Glycemic and Lipid Parameters in Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Pilot Study. Diabetes Care. 2016 Oct;39(10):1777-86.
57. Naftali T, Mechulam R, Marii A, et al. Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial. Dig Dis Sci. 2017 Jun;62(6):1615-1620.
58. Masataka N. Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers With Social Anxiety Disorders. Front Psychol. 2019;10:2466.
59. Ghodke-Puranik Y, Thorn CF, Lamba JK, et al. Valproic Acid Pathway: Pharmacokinetics and Pharmacodynamics. Pharmacogenet Genomics. 2013;23(4): 236-241.
60. Morrison G, Crockett J, Blakey G, Sommerville K. Pharmacokinetic Trial to Investigate Possible Drug-Drug Interactions Between Clobazam, Stiripentol, or Valproate and Cannabidiol in Healthy Subjects. Clinical Pharmacology in Drug Development 2019;8(8):1009–1031.
61. Landmark CJ, Brandl U. Pharmacology and drug interactions of cannabinoids. Epileptic Disord 2020;22(Suppl. 1):S16-S22.

Figure legends

Figure 1. Proportion of serious adverse effects (SAEs) related to cannabidiol (CBD) use in different samples.

Figure 2. Proportion of serious adverse effects (SAEs) related to cannabidiol (CBD) use with different drugs.

Table 1. Summary of the randomized controlled trials (RCTs) with canabidiol (CBD) in healthy volunteers.

Reference	Sample	Treatment	Time	Main Safety Outcomes	Severe or Serious Adverse Effects in CBD group		Concomitant Medications
					Number	Reported by the authors	
Cunha et al. 1980 (42)	16 healthy adults	3 mg/kg/day oral CBD (n=8) or placebo (n=8) Plant-derived formulation of CBD in crystalline form (Makor Chemicals, Jerusalem) administered in gelatin capsules + CBD isolated from hashish administered in gelatin capsules	30 days	Neurological and clinical examination, EEG, ECG, blood and urine analysis, self-report	0	None	None
Taylor et al. 2018 (43)	24 healthy adults	750 oral CBD (n=9) or 1500 mg (n=9) or placebo (n=6; 3 per CBD dose group)	1 week	Neurological and clinical examination, EEG, ECG, blood and urine analysis, sleep, suicidality,	0	None	None

		Plant-derived pharmaceutical formulation of purified CBD (GW Pharmaceuticals, United Kingdom) administered in oral solution (FDA-approved: Epidiolex®)		withdrawal symptoms			
Taylor et al. 2020 (44)	30 healthy adults in part 1 (open-label) and 21 in part 2 (double-bind)	Part 1 – 750 mg oral CBD twice daily (1500 mg/day); Part 2 – CBD (n=9) or placebo (n=12) Plant-derived pharmaceutical formulation of purified CBD (GW Pharmaceuticals, United Kingdom) administered in oral solution (FDA-approved: Epidiolex®)	Part 1 – 28 days Part 2 – 2 weeks	Clinical laboratory tests, vital signs, ECG, physical examinations, sleep, suicidality, depression, withdrawal symptoms	0	None	None

Sultan et al. 2020 (45)	26 health adults	600 mg oral CBD (n=13) and placebo (n=13)	1 week	Cardiovascular parameters, self-report	0	None	None

CBD, cannabidiol; ECG, electrocardiogram; EEG, electroencephalography; FDA, Food and Drug Administration.

Table 2. Summary of the randomized controlled trials (RCTs) with canabidiol (CBD) in epileptic patients.

Reference	Sample	Treatment	Time	Main Safety Outcomes	Serious Adverse Effects in CBD group		Concomitant Medications
					Number	Reported by the authors	
Cunha et al. 1980 (42)	15 adults with secondary generalized epilepsy with temporal lobe focus unresponsive to anti-epileptic drugs	Add-on 200–300 mg/day oral CBD (n=8) or placebo (n=7) for 8–18 weeks Plant-derived formulation of CBD in crystalline form (Makor Chemicals, Jerusalem) administered in gelatin capsules + CBD isolated from hashish administered in gelatin capsules	8–18 weeks	Neurological and clinical examination, EEG, ECG, blood and urine analysis, self-report	0	None	Comital, gardenal, hidantal, primidona, clonazepam, fenobarbital, tegretol, mysoline
Devinsky et al. 2017 (46)	120 children and young adults with Dravet syndrome (drug-resistant	Add-on 20 mg/kg/day oral CBD (n=61) or placebo (n=59) for 14	14 weeks (2 weeks of dose escalation and 12 weeks of	Clinical examination, vital signs, ECG, suicidality,	10	**- Status epilepticus** **- Elevated**	Clobazam, valproate, stiripentol, levetiracetam,

	epilepsy)	weeks Plant-derived pharmaceutical formulation of purified CBD (GW Pharmaceuticals, United Kingdom) administered in oral solution (FDA-approved: Epidiolex®)	dose maintenance)	laboratory assessments (hematology, biochemistry, and urinalysis)		**transaminase**s	topiramate
Devinsky et al. 2018a (47)	34 with Dravet syndrome	Add-on 5, 10, or 20 mg/kg/day oral CBD (n=8-10 per dose) or placebo (n=7) Plant-derived pharmaceutical formulation of purified CBD (GW Pharmaceuticals, United Kingdom) administered in oral solution (FDA-approved: Epidiolex®)	3 weeks	Clinical examination, vital signs, ECG, suicidality, laboratory assessments (hematology, biochemistry, and urinalysis)	4	**- Pyrexia** **- Rash** **- Convulsion** **- Elevated transaminase**s	Clobazam, valproate, stiripentol, levitiracetam, topiramate

Devinsky et al. 2018b (48)	225 patients with Lennox–Gastaut syndrome	Add-on 10 (n=73) or 20 (n=76) mg/kg/day oral CBD or placebo (n=76) Plant-derived pharmaceutical formulation of purified CBD (GW Pharmaceuticals, United Kingdom) administered in oral solution (FDA-approved: Epidiolex®)	14 weeks (2 weeks of dose escalation and 12 weeks of dose maintenance)	Clinical examination, vital signs, ECG, suicidality, laboratory assessments (hematology, biochemistry, and urinalysis)	26	**- Elevated transaminases** **- Elevated γ-glutamyltransferase** - **Somnolence** **- Increased seizures** - N**onconvulsive status epilepticus** **- Lethargy** **- Constipation** - **Worsening chronic cholecystiti**s	Clobazam, valproate, levetiracetam, lamotrigine, rufinamide
Thiele et al. 2018 (49)	171 patients with Lennox–Gastaut syndrome	Add-on 20 mg/kg/day oral CBD (n=86) or placebo (n=85) for 14 weeks (2 weeks of dose escalation and 12 weeks of dose maintenance)	14 weeks (2 weeks of dose escalation and 12 weeks of dose maintenance)	Clinical examination, vital signs, ECG, suicidality, laboratory assessments	20	**- Elevated transaminases** - **Elevated γ-glutamyltransferase** **- Convulsion**	Clobazam, valproic acid, lamotrigine, levetiracetam, rufinamide

		Plant-derived pharmaceutical formulation of purified CBD (GW Pharmaceuticals, United Kingdom) administered in oral solution (FDA-approved: Epidiolex®)		(hematology, biochemistry, and urinalysis)		**- Rash** **- Lethargy** **- Pneumonia** **- Respiratory failure (1 death)** **- Diarrhea** **- Vomiting** **- Viral infection** **- Increased concentration of AED** **- Restlessness** **- Hypercapnia** **- Hypoxia**	
Miller et al., 2020 (50)	198 patients with Dravet syndrome	Add-on 10 mg/kg/day oral CBD (n=66), 20 mg/kg/day oral CBD (n=67) or placebo (n=65)	14 weeks (2 weeks of dose escalation and 12 weeks of dose	Clinical examination, laboratory assessments (hematology, biochemistry, and	30	Not reported	Valproate, clobazam, stiripentol, levetiracetam, topiramate, felbamate,

			maintenance)	urinalysis)			carbamazepine

AED, antiepileptic drug; CBD, cannabidiol; DILI, drug-induced liver injury; ECG, electrocardiogram; EEG, electroencephalography; FDA, Food and Drug Administration; HDL, high-density lipoprotein; N-CLB, N-desmethylclobazam; NIDA, National Institute on Drug Abuse.

Table 3. Summary of the randomized controlled trials (RCTs) with canabidiol (CBD) in other clinical samples.

Reference	Sample	Treatment	Time	Main Safety Outcomes	Serious Adverse Effects in CBD group		Concomitant Medications
					Number	Reported by the authors	
Consroe et al. 1991 (51)	15 neuroleptic-free adults with Huntington's disease	10 mg/kg/day oral CBD (n=8) or placebo (n=7)	6 weeks	BP/HR, blood and urine analysis, prolactin	0	None	None
Leweke et al, 2012 (52)	39 adults with schizophrenia or schizophreniform psychosis	800 mg/day oral CBD (n=20) or amisulpride (n=19)	4 weeks	Extrapyramidal symptoms, serum prolactin, body weight, ECG, hepatic function, blood parameters	0	None	Lorazepam
Chagas et al., 2014 (53)	21 adults with Parkinson's disease without dementia or comorbid psychiatric	Add-on 75 (n=7) or 300 (n=7) mg/day oral CBD or placebo (n=7)	6 weeks	Self-report (psychic, neurologic, autonomic and other manifestations)	0	None	Typical antiparkinsonian drugs

	conditions						
Boggs et al. 2018 (54)	36 adults with chronic schizophrenia	Add-on 600 mg/day oral CBD (n=18) or placebo (n=18)	6 weeks	Mood, suicidality, sedation, motor effects	1	**- Sedation**	Multiple antipsychotics (first and second generation, long-acting/injectable antipsychotics), antidepressants, anticholinergic, anticonvulsants/mood stabilizers, benzodiazepines
McGuire et al. 2018 (55)	88 adults with chronic schizophrenia	Add-on 1000 mg/day oral CBD (n=43) or placebo (n=45)	6 weeks	Extrapyramidal symptoms, body weight, ECG, waist circumference, hepatic function, prolactin, inflammatory markers, HDL cholesterol	1	**- Gastrointestinal disorder (nausea, diarrhea, abdominal pain, and vomiting)**	Aripiprazole, olanzapine, risperidone, amisulpride, quetiapine, flupentixol, clozapine, zuclopentixol acetate, paliperidone, ziprasidone

Jadoon et al. 2016 (56)	27 subjects with noninsulin-treated type 2 diabetes	Add-on 100 mg oral CBD twice daily (n=13) or placebo (n=14)	13 weeks	Vital signs, ECG, anxiety, depression	0	None	Metformin, sulfonylureas, dipeptidyl, peptidase-4 inhibitors, statins
Naftali et al. 2017 (57)	19 treatment-resistant patients with Crohn's disease	Add-on 10 mg oral CBD twice daily (n=10) or placebo (n=9)	8 weeks	Self-report, blood count, liver and kidney function, CRP	0	None	5-ASA drugs, steroids, immunomodulators, methotrexate, TNF antagonists
Masataka, 2019 (58)	37 young adults with SAD	300 mg oral CBD (n=17) or placebo (n=20) daily for 4 weeks	4 weeks	Self-report	0	None	None

BP/HR, blood pressure/heart rate; CBD, cannabidiol; CRP, C-reactive protein; ECG, electrocardiogram; HDL, high-density lipoprotein; NIDA, National Institute on Drug Abuse; RCT, randomized clinical trial; SAD, social anxiety disorder; THC, tetrahydrocannabinol; TNF, tumor necrosis factor; 5-ASA, 5-aminosalicylic acid.

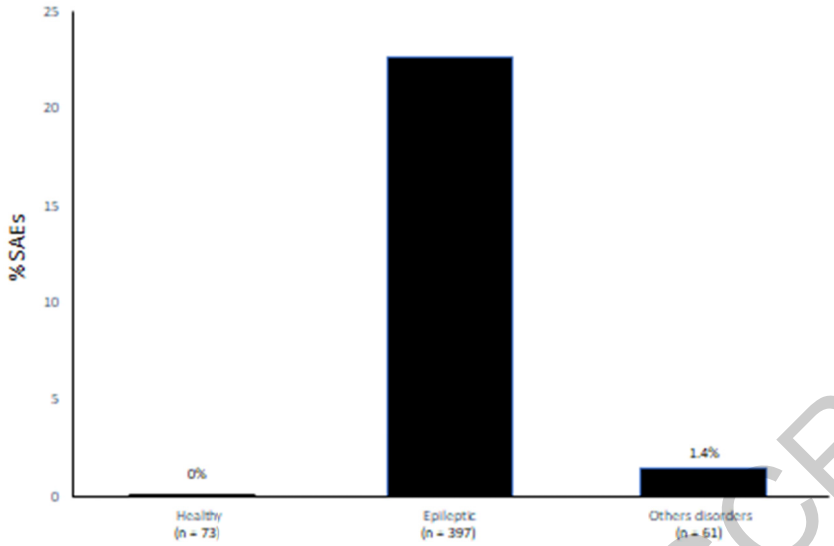

Figure 1

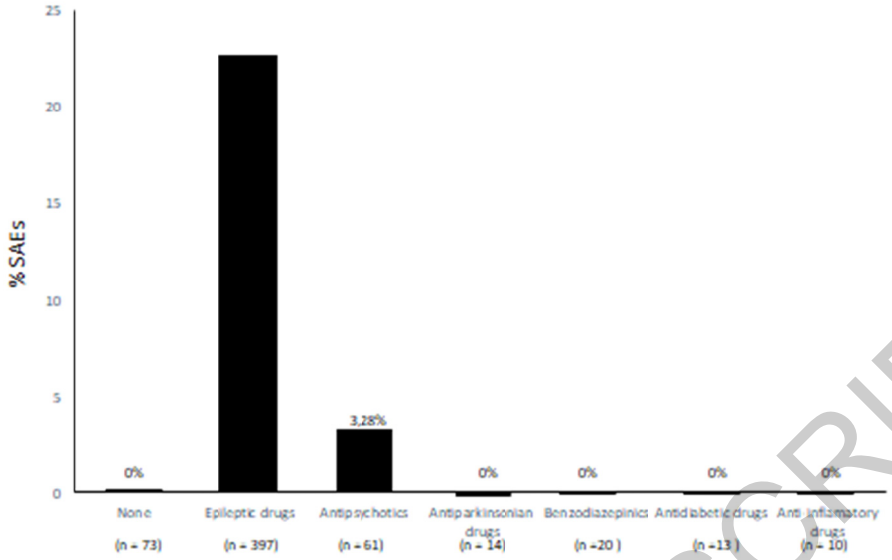

Figure 2