

Adverse effects of cannabinoids

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ABSTRACT – Cannabidiol is a cannabinoid-derived product that has recently been approved for the treatment of pharmacoresistant seizures in patients with epileptic encephalopathies such as Dravet Syndrome and Lennox-Gastaut Syndrome. Short-term side effects of cannabidiol are well known and well-documented in the clinical trials that lead to its approval. Generally, is a well tolerated drug with transitory, dose-dependent mild to moderate effects like somnolence, decreased appetite or diarrhoea. However severe life-threatening reactions can also occur, and are often related to the non-controlled toxic combination with other antiseizure drugs that are widely used in this type of patients like sodium valproate or clobazam. In this brief review we summarize the available data about the short-term adverse events of cannabidiol. Further studies are required to assess the long-term outcome and final resolution of these conditions regarding safety of these patients.

Key words: cannabidiol, clinical trials, side effects, adverse reactions, Epidiolex, Epidyolex

Cannabis sativa contains more than 80 phytocannabinoids, but little is known about the potential therapeutic effects of most of these molecules. One compound, cannabidiol (CBD) is present at high concentrations in the plant and has demonstrated antiepileptic properties. The medical use of whole-plant cannabis extract is limited by the THC-induced psychoactive properties and the long-term cognitive side effects associated with chronic use (Devinsky, 2016). Safety data published for CBD-containing compounds in adults with different neurological disorders by Koppel *et al.* (2014) was followed by clinical trials, leading to the approval of a high-CBD-concentration oral solution

(Epidiolex) for treatment of seizures in patients with Dravet syndrome and Lennox-Gastaut syndrome by the Food and Drug Administration in June 2018 and European Medicines Agency in July 2019.

Short and long-term adverse events of CBD reported in clinical trials

Adverse effects of CBD in patients with treatment-resistant epilepsy are well-documented in randomized and open-label trials. In the first specific double-blinded randomized trial for CBD in children with Dravet syndrome (DS) (Devinsky *et al.*, 2017), adverse events (AEs)



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were reported in 93% of patients in the CBD group compared to 75% in the placebo group. Most of them (89%) were mild or moderate, appeared in the two-week escalation period, and in two thirds resolved in the first four weeks of treatment. In most patients with DS, the maximal CBD tolerable dose is 20 mg/kg/day (McCoy *et al.*, 2018) and side effects seem to be positively correlated with higher doses of CBD. Most commonly reported CBD AEs include somnolence (22%), diarrhoea (19%), and decreased appetite (17%). Other less frequent AEs include vomiting, fatigue, weight loss, pyrexia, and upper respiratory tract infections. This was consistently found in subsequent clinical trials exploring tolerability of different doses of CBD (Devinsky *et al.*, 2018a, 2018b).

Serious adverse events appear in around 15% of patients treated with CBD. The most significant is the harmful elevation (three times the upper the normal limit) of alanine transaminase (ALT) and aspartate transaminase (AST) levels. Elevation of liver enzymes is also more frequent on high doses of CBD (20 mg/kg/day) and concomitant treatment with valproic acid (Devinsky *et al.*, 2019). Rash has rarely been reported but can appear in association with pyrexia and may lead to discontinuation of the drug (Devinsky *et al.*, 2018a).

When starting a new antiepileptic drug for DS, consideration of the potential pharmacological interactions between given medications is necessary, especially with clobazam (Johannessen Landmark and Brandl, 2020). CBD undergoes significant metabolism via different isoforms of the cytochrome (CYP) P-450 metabolic pathways, CYP 2C9 and 3A4 (Stout and Cimino, 2014), and at the same time constitutes a potent inhibitor of both enzymes. Clobazam metabolism similarly involves CYP 3A4 and in a minor way, CYP 2C19; both of these enzymes catalyse the metabolism of its active metabolite, N-desmethylclobazam (norclobazam; N-CLB) (Geffrey *et al.*, 2015). Uncontrolled studies have shown that the level of N-CLB is increased by CBD, which might lead to a synergistic antiepileptic effect as well as an increase in the rate of AEs in patients taking both drugs, especially somnolence. Phenotypic variability of CYP 2C19 due to polymorphisms can produce variations in N-CLB in patients taking not only CBD but also different antiepileptic drugs that are also metabolic substrates of the CYP-450 pathway. Measurement of serum N-CLB concentrations can be clinically useful for the identification of vulnerable individuals with unexpected moderate and severe AEs (Yamamoto *et al.*, 2013). Surprisingly, elevation of N-CLB in patients taking CBD does not occur in the presence of stiripentol, a strong inhibitor of CYP 2C19, which may interfere with clobazam metabolism (Devinsky *et al.*, 2018a). This is probably explained by normalization of N-CLB levels

due to drug dose adjustments prior to the initiation of CBD. There is no apparent significant pharmacokinetic effect between CBD and other concomitant AEDs (valproate, topiramate, levetiracetam, rufinamide, lamotrigine, felbamate or zonisamide) (Gaston *et al.*, 2017). Most of the AEs in patients with LGS taking CBD are similar to those reported in the DS trials. However, when looking at raw data in the CBD pivotal trials, AEs seem to be more frequent in the DS sample than in LGS. In the study by Devinsky *et al.* (2018b) for CBD as an add-on treatment for drug-resistant seizures in LGS, three branches of treatment were included: a 20 mg/kg/day group, a 10 mg/kg/day group, and a placebo group. In the 20 mg/kg/day CBD group, several observed adverse events had a similar incidence in both DS and LGS studies: somnolence was observed in 36% vs. 30%, decreased appetite in 28% vs. 26%, vomiting in 15% vs. 12%, and pyrexia in 15% vs. 12% in DS and LGS patients, respectively. More strikingly, diarrhoea was more common in DS (31%) than in LGS (13%). This difference may be explained by age differences between both subgroups (2-55 years in the LGS group vs. 2-18 years in the DS group), differences in background medications, or, less likely, a disease-specific vulnerability for the drug.

Some very infrequent AEs were reported in patients with LGS taking CBD, such as elevation of γ -glutamyltransferase concentration, increased seizure frequency during weaning-off medication, constipation, and worsening of previous chronic cholecystitis. Elevation of serum transaminases was also a serious adverse event in the pivotal trial, however, none of the patients met the criteria for severe drug-induced liver injury. Most of these AEs occurred within the first 30 days of treatment (Lattanzi *et al.*, 2018) and were reported in patients on high CBD doses as well as valproic acid (Thiele *et al.*, 2018).

Few data are available to assess the safety profile of CBD for epileptic syndromes other than DS and LGS. The first open-label interventional trial for CBD for several types of drug-resistant epilepsy by Devinsky *et al.* (2016) included a wide heterogeneous group of patients with epilepsy due to different aetiologies (from *CDKL5* mutations or Aicardi syndrome to generalized epilepsies such as Jeavons's syndrome). Post-hoc analysis was made only for patients with DS and LGS difficult to extrapolate to other types of epilepsy (table 1). However, in this trial in which doses of CBD were raised up to 50 mg/kg/day, some serious AEs were reported in patients concomitantly taking valproate, such as severe hyperammonaemia that led to CBD discontinuation or severe thrombocytopenia which resolved when valproate was stopped. The relationship between hyperammonaemia and other adverse events has not been systematically assessed in other

Table 1. Adverse events reported by Devinsky *et al.* (2016) based on an open-label study of 214 patients, aged 1-30 years, with drug-resistant epilepsy.

	Safety analysis group (n=162)
Adverse events (reported in >5% patients)	
Somnolence	41 (25%)
Decreased appetite	31 (19%)
Diarrhoea	31 (19%)
Fatigue	21 (13%)
Convulsion	18 (11%)
Increased appetite	14 (9%)
Status epilepticus	13 (8%)
Lethargy	12 (7%)
Weight increased	12 (7%)
Weight decreased	10 (6%)
Drug concentration increased	9 (6%)
Treatment-emergent serious adverse events*	
Status epilepticus	9 (6%)
Diarrhoea	3 (2%)
Weight decreased	2 (1%)
Convulsion	1 (<1%)
Decreased appetite	1 (<1%)
Drug concentration increased	1 (<1%)
Hepatotoxicity	1 (<1%)
Hyperammonaemia	1 (<1%)
Lethargy	1 (<1%)
Unspecified pneumonia	1 (<1%)
Aspiration pneumonia	1 (<1%)
Bacterial pneumonia	1 (<1%)
Thrombocytopenia	1 (<1%)

Data are presented as *n* (%). One patient might have had more than one serious adverse event.

*Reported by the investigator to be possibly related to CBD use.

studies, leaving some areas for improvement in AE identification and management in the future.

Efficacy of CBD for pharmaco-resistant epilepsy in patients with tuberous sclerosis complex has been studied in a small non-controlled trial of 18 patients in which CBD was added, up to 50 mg/kg/day to their regular antiepileptic therapy (Hess *et al.*, 2016). The most frequent observed AE was drowsiness (44%) followed by ataxia (27.8%) and diarrhoea (22.2%); none of these AEs were considered serious by the investigators. Interestingly, most patients experiencing AEs were taking clobazam and were less likely to reach the high target dose of the study, requiring dose adjustments of either CBD or clobazam to reduce the intensity of the AEs. A small non-placebo, controlled trial to assess the efficacy of CBD in seven paediatric patients with febrile infection-related epilepsy (FIRES) is also documented and reveals mild side effects that

include dizziness, decreased appetite, weight loss, and nausea/vomiting (Gofshteyn *et al.*, 2017).

Conclusions

Compared to other antiseizure drugs approved for treatment of DS and LGS, more information was available prior to marketing for CBD (Epidiolex/Epidyolex). CBD is generally a well-tolerated drug, with most AEs being mild or moderate and improving either with treatment maintenance or reduction of dosage (Arzimanoglou *et al.*, 2020). The most frequent AEs include somnolence, decreased appetite, and diarrhoea. Most of the side effects occur at the beginning of treatment with doses above 20 mg/kg/day. Prior to starting CBD, a careful assessment of concomitant antiepileptic drugs should be performed, particularly valproic acid, as this combination with CBD is associated with transaminase elevation and decreased platelet count. Also, clobazam, jointly administered with CBD, may produce an increase in somnolence due to nor-clobazam elevation. Additional studies are necessary to identify the reasons for gastrointestinal side effects and provide alternatives to improve the tolerance of CBD in these patients. □

Disclosures.

Antonio Gil-Nagel has received speaker honoraria and served as advisor for Eisai, GW Pharma, UCB Pharma, and Zogenix.

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TEST YOURSELF



(1) In which circumstances is it more likely that a significant transaminase elevation occurs during initiation of CBD treatment?

- A. In patients concomitantly treated with valproic acid
- B. In patients with Dravet syndrome
- C. In patients concomitantly treated with clobazam
- D. In patients additionally treated with more than two AEDs
- E. In all of the above

(2) In which circumstances can we expect to observe more sedation following the addition of CBD?

- A. In patients already on stiripentol and clobazam
- B. In patients with Lennox-Gastaut syndrome
- C. In patients concomitantly treated with clobazam but not on stiripentol
- D. In patients with Dravet syndrome
- E. In patients on topiramate

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".