U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Cannabidiol. [Updated 2019 Apr 12].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Cannabidiol

Updated: April 12, 2019.

OVERVIEW

Introduction

Cannabidiol is an orally available cannabinoid that is used to treat patients with refractory epilepsy due to Lennox-Gastaut or Dravet syndrome. Cannabidiol is associated with frequent serum enzyme elevations during therapy particularly with higher doses but has not been linked to cases of clinically apparent liver injury with jaundice.

Background

Cannabidiol (kan" a bi dye' ol) is a natural cannabinoid, the second most common component in Cannabis sativa. Unlike the most abundant cannabinoid delta-9-tetrahydrocannabinol (THC), the psychoactive ingredient of marijuana, cannabidiol has minimal psychoactive properties and actually decreases the risk of psychotic symptoms and impaired cognition after cannabis use. The mechanism of action of cannabidiol is unknown, but it may be a partial agonist of cannabinoid receptors. Cannabidiol was found to improve symptoms in schizophrenia and to reduce the frequency of seizures in treatment-resistant epilepsy, particularly in those with Lennox-Gastaut or Dravet syndrome, two rare but severe childhood-onset forms of epilepsy. Cannabidiol was approved for use in the United States in 2018. Current indications are limited to treatment of seizures associated with Lennox-Gastaut or Dravet syndrome in adults and in children above the age of two. Cannabidiol is available as an oral solution of 100 mg/mL under the brand name Epidiolex. The typical dose is 2.5 mg/kg twice daily, which can be increased based upon tolerance and effect to 5 mg/kg twice daily and to a maximum of 10 mg/kg twice daily. The dose should be reduced in patients with pre-existing hepatic impairment. Side effects are mostly dose related and can include fatigue, somnolence, dizziness, sleep disturbance, insomnia, anorexia, weight loss, diarrhea, infections and rash. Rare, but potentially severe side effects include marked sedation and somnolence, suicidal behavior and ideation and hypersensitivity reactions. Cannabidiol is generally used in combination with other anticonvulsants and is prone to drug-drug interactions that may affect drug levels and side effects of those agents, particularly valproate and clobazam.

Hepatotoxicity

In prelicensure studies, serum aminotransferase elevations arose during cannabidiol therapy in 34% to 47% of patients compared to 18% of controls who were receiving other anticonvulsant medications. Elevations above 3 times ULN occurred in 13% of cannabidiol treated compared to 1% on placebo. ALT and AST elevations were more frequent with higher doses and were particularly common (and sometimes delayed) in patients who were receiving valproate and clobazam. The aminotransferase elevations typically arose within the first two months of treatment and were transient, mild-to-moderate in severity, and not associated with symptoms or jaundice.

There have been no convincing reports of clinically apparent liver injury with jaundice attributable to cannabidiol, but it has had very limited general use.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of serum aminotransferase elevations during cannabidiol therapy is not known but may be due to production of a toxic intermediate in its metabolism. Cannabidiol is metabolized by the liver in large part by CYP 3A4 and is susceptible to drug-drug interactions with agents that induce or inhibit CYP 3A4 activity.

Mechanism of Injury

Cannabidiol therapy is associated serum ALT and AST elevations that generally arise within the first 2 months of treatment and are mild-to-moderate in severity. The frequency of elevations is dose related and more frequent with concurrent use of valproate and clobazam. The elevations, however, are generally asymptomatic, self-limited in course and not associated with jaundice. Nevertheless, routine monitoring of liver tests is recommended before starting and at 1, 3 and 6 months during treatment as well as periodically thereafter, particularly in patients who are also receiving valproate. Cannabidiol should be discontinued if there are ALT elevations accompanied by symptoms of jaundice or if the levels rise and persist at more than 5 times ULN.

Drug Class: Anticonvulsants; Dronabinol

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Cannabidiol – Epidiolex®

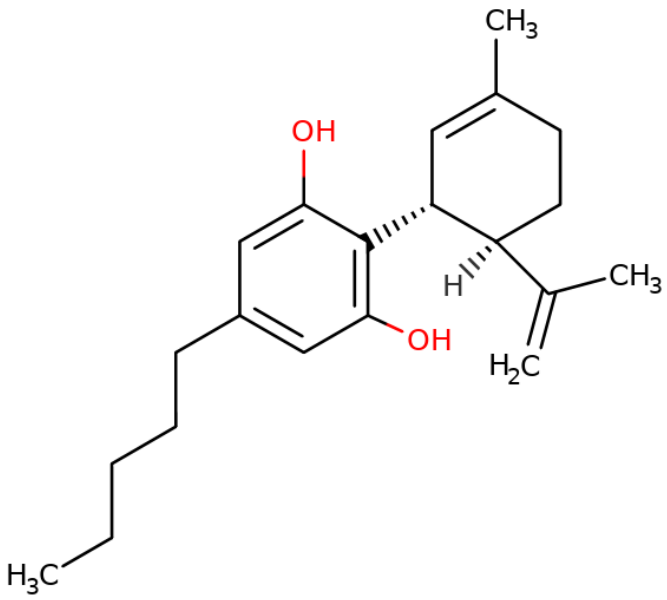
DRUG CLASS

Anticonvulsants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Cannabidiol	13956-29-1	C21-H30-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 12 April 2019

Zimmerman HJ. Antiemetic and prokinetic compounds. Miscellaneous drugs and diagnostic chemicals. In, Hepatotoxicity: The adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 1999, p. 721.

(Expert review of hepatotoxicity published in 1999 does not discuss cannabidiol).

Smith MD, Metcalf CS, Wilcox KS. Pharmacotherapy of the epilepsies. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 303-26.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; cannabidiol caused dose related elevations in ALT arising in 52% of patients and to above 5 times ULN in 6%, occurring most frequently when given with valproate and sometimes with delayed onset which was most frequent when given with valproate, but no case was associated with concurrent significant bilirubin elevations).

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; cannabidiol caused dose related elevations in ALT arising in 52% of patients and to above 5 times ULN in 6%, occurring most frequently when given with

valproate and sometimes with delayed onset which was most frequent when given with valproate, but no case was associated with concurrent significant bilirubin elevations).

Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, Miller I, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016; 15: 270-8. PubMed PMID: 26724101.

(Among 162 patients [ages 1–30 years] with intractable, childhood-onset epilepsy who were treated with cannabidiol for at least 12 weeks, the frequency of seizures decreased by 37% while adverse events included somnolence [25%], anorexia [19%] diarrhea [19%], fatigue [13%] and elevated liver tests [7%] which led to early discontinuation in patients on valproate).

McGuire P, Robson P, Cubala WJ, Vasile D, Morrison PD, Barron R, Taylor A, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry 2018; 175: 225-31. PubMed PMID: 29241357.

(Among 88 patients with schizophrenia in a placebo controlled trial for 6 weeks, clinical improvements were more frequent with cannabidiol [1000 mg daily] than placebo, while adverse event rates were more frequent including diarrhea [9% vs 4%] and nausea [7% vs 0%]).

Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, et al.; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018; 391 (10125): 1085-96. PubMed PMID: 29395273.

(Among 171 patients with treatment resistant seizures due to Lennox-Gastaut syndrome in a 14-week placebo controlled trial, seizure frequency decreased by 44% with cannabidiol vs 22% in controls and side effects included diarrhea [19% vs 8%], somnolence [15% vs 9%], fatigue [6% vs 2%] and ALT elevations [9% vs 2%]).

Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, Greenwood S, et al; GWPCARE1 Part A Study Group. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology 2018; 90: e1204-e1211. PubMed PMID: 29540584.

(Among 34 patients with refractory seizures due to Dravet syndrome treated with cannabidiol [5, 10 or 20 m/kg/day] or placebo, 6 of 27 [22%] on cannabidiol developed ALT elevations above 3 times ULN [all on valproate], which resolved in all but led to early drug discontinuation in one subject).

Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, et al.; GWPCARE3 Study Group. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med 2018; 378: 1888-97. PubMed PMID: 29768152.

(Among 225 patients [ages 2 to 55 years] with refractory drop seizures due to Lennox-Gastaut syndrome in a 14-week placebo controlled trial, seizure frequency decreased more with cannabidiol [37% at 10 mg and 42% at 20 mg per kg daily] than placebo [17%], while adverse events were more frequent including somnolence [21-30% vs 5%], anorexia [16-26% vs 8%] and diarrhea [10-15% vs 8%] and ALT elevations were the most common reason for drug discontinuation, although no patient developed clinically apparent liver injury or jaundice).

Szaflarski JP, Bebin EM, Comi AM, Patel AD, Joshi C, Checketts D, Beal JC, et al.; CBD EAP study group. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results. Epilepsia 2018 Jul 12. [Epub ahead of print] PubMed PMID: 29998598.

(Among 607 patients [ages <1 to 62 years] with treatment-resistant epilepsy treated with cannabidiol in an expanded access program with median treatment of 48 weeks, seizure frequency decreased by 51% and common adverse events were diarrhea [29%], somnolence [22%], anorexia [12%] and fatigue [11%]; ALT or AST elevations above 3 times ULN arose in 61 subjects [10%], most of whom [n=46] who were also receiving valproate, but there were no instances of clinically apparent liver injury).

Thiele E, Marsh E, Mazurkiewicz-Beldzinska M, Halford JJ, Gunning B, Devinsky O, Checketts D, et al. Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. Epilepsia 2019; 60: 419-28. PubMed PMID: 30740695.

(Among 366 patients who completed controlled trials of cannabidiol for Lennox-Gastaut syndrome and continued therapy for an average of 38 weeks, adverse events included diarrhea [27%] and somnolence [24%] while ALT or AST elevations above 3 times ULN arose in 21% of patients also receiving valproate but only 3.5% of those who were not, and no patient developed clinically apparent liver injury with jaundice although 1.5% stopped therapy because of ALT or AST elevations).