



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Cannabidiol

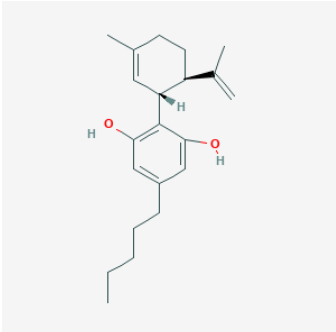
Evidence Summary

Preclinical evidence is strong for Alzheimer's disease, cardiovascular disease, and cancer, but evidence from long-term well-designed clinical trials is lacking. May increase liver enzymes.

Neuroprotective Benefit: Preclinical evidence is strong for neuroprotection, but none of the clinical studies have shown strong cognitive benefits. No data exist for long-term treatment in healthy adults.

Aging and related health concerns: Numerous preclinical studies exist for various indications, including protection from stroke, atherosclerosis, cancer, and neuropathy, but no evidence from high quality, well-designed clinical trials in humans exist thus far.

Safety: Mild adverse events are common, including somnolence, decreased appetite, gastrointestinal issues, and increased liver enzymes. Some drug interactions are known (e.g., cilostazol, citalopram, clopidogrel, flibanserin).

<p>Availability: Epidiolex®, available with prescription for Lennox-Gastaut syndrome and Dravet syndrome</p>	<p>Dose: in seizure patients, initially 2.5 mg/kg twice daily, then increased to 5 mg/kg twice daily (max dose 10 mg/kg, twice daily)</p>	<p>Chemical formula: C₂₁H₃₀O₂ MW: 314.464</p>
<p>Half life: 1-2 hours for elimination from plasma; terminal elimination half-life between 56-61 hours</p>	<p>BBB: penetrant</p>	
<p>Clinical trials: a meta-analysis in an epilepsy population included 2 RCTs with a total of 396 patients</p>	<p>Observational studies: none that specifically examine cannabidiol</p>	

What is it? Cannabidiol is one of at least 85 active cannabinoids identified in the Cannabis plant. Cannabidiol binds to a wide variety of targets of the endocannabinoid system, though the precise mechanisms of action are currently being investigated ([DrugBank.ca](#)). The anticonvulsant action of cannabidiol is not thought to involve its effects on cannabinoid receptors ([Drugs.com](#)). In 2018, cannabidiol (Epidiolex®) was approved by the FDA for two rare forms of childhood epilepsy—Lennox-Gastaut syndrome and Dravet syndrome. It is the first FDA-approved cannabidiol-based product available in the US. People also take cannabidiol-containing products for anxiety, bipolar disorder, dystonia (a muscle disorder), multiple sclerosis, Parkinson’s disease, and schizophrenia ([WebMD.com](#)).

Despite being a cannabinoid, cannabidiol has very low affinity for both CB1 and CB2 receptors and probably exerts no direct effect at CB2 receptors [1]. However, cannabidiol shows “functional” antagonism of CB1 receptors, possibly through negative allosteric modulation. Cannabidiol increases circulating endocannabinoids through inhibition of the enzyme FAAH (fatty acid amide hydrolase). Cannabidiol appears to have pleiotropic effects outside of the endocannabinoid pathway. It can act as a positive modulator of serotonin 1A receptor-mediated neurotransmission or as an agonist at TRPV1 and PPAR γ receptors [2]. Cannabidiol can facilitate anandamide (an omega-6 polyunsaturated fatty acid)-mediated neurotransmission (by inhibiting the enzyme FAAH) and induce antioxidant actions. Cannabidiol also promotes a complex set of changes in signaling pathways such as mTOR, autophagy, and GSK3 β , resulting in neuroprotection, decreased proinflammatory responses, and facilitation of neuroplastic events [2].



Recreational use of cannabis seldomly causes permanent psychological disorders depending on the individual's sensitivity, including cognitive impairment, anxiety, paranoia, and increased risks of psychosis or drug addiction [3]. Tetrahydrocannabinol (THC) appears to be responsible for many of the negative effects, while cannabidiol has been shown to counteract these negative effects (e.g., anxiogenic effects).

Neuroprotective Benefit: Preclinical evidence is strong for neuroprotection, but none of the clinical studies have shown strong cognitive benefits. No data exist for long-term treatment in healthy adults.

Types of evidence:

- 2 meta-analyses, 1 in epilepsy and 1 in schizophrenia
- 6 randomized controlled trials
- 1 open-label clinical trial
- 2 neuroimaging studies in humans
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

No studies have tested whether cannabidiol can prevent dementia or cognitive decline.

Healthy adults: NO COGNITIVE BENEFIT BUT MAY DECREASE ANXIETY. In a double-blind randomized controlled trial of 27 healthy adults, cannabidiol treatment (300 mg) for 2 days did not induce any significant effects on cognitive measures (measured by digit symbol substitution, symbol copying tests, and psychomotor vigilance test) or mood (Visual analog mood scale, State-Trait anxiety inventory)[4]. A smaller double-blind randomized controlled trial of 10 healthy adults reported that a single dose of cannabidiol (400 mg) significantly decreased subjective anxiety and increased mental sedation [5]. Based on measures of regional cerebral blood flow (SPECT), cannabidiol's anxiolytic properties may be mediated by an action on limbic and paralimbic brain areas. Given the limited spatial resolution of SPECT, interpretation needs to be made with caution.

Epilepsy patients: COGNITIVE BENEFIT UNKNOWN. The largest study (meta-analysis) was carried out in patients with Lennox-Gastaut syndrome, a form of epilepsy [6]. This study included 2 randomized controlled trials enrolling a total of 396 patients. Cannabidiol as adjunctive treatment (5-20 mg/kg, twice



daily) for 3-14 weeks significantly reduced seizure frequency compared to placebo. However, cognitive outcomes were not included in these studies.

Huntington's disease patients: NO BENEFIT. In a small double-blind randomized controlled trial of 15 Huntington's disease patients, cannabidiol treatment (10 mg/kg/day) for 6 weeks was neither symptomatically effective nor harmful, relative to placebo [7]. Direction of treatment responses for chorea severity appeared to favor cannabidiol but the difference was small and not significant ($p=0.7$).

Schizophrenia patients: MIXED BENEFIT. A 2017 systematic review of the effects of cannabidiol and/or THC in schizophrenia included 9 clinical and 18 preclinical studies [8]. One clinical investigation testing the effects of cannabidiol on cognition in schizophrenia patients showed negative results for the Stroop test. Cannabidiol does appear to attenuate THC-induced cognitive deficits. Of 9 clinical trials with a total of 21 cognitive domains tested, a few improvements were seen, including recognition memory, verbal learning and memory, and social recognition; however, treatments were not specific to cannabidiol. For all other measures, cannabidiol (and/or THC, etc.) did not affect cognitive functions.

There are two newer randomized controlled trials testing cannabidiol specifically in schizophrenia patients [9; 10]. One double-blind trial included 88 schizophrenia patients, and treatment with cannabidiol (1000 mg/day) for 6 weeks resulted in lower levels of psychotic symptoms and patients were more likely to have been rated as improved (CGI-I: treatment difference=-0.5, 95% CI, -0.8 to -0.1)[10]. Patients who received cannabidiol also showed greater improvements that fell short of statistical significance in cognitive performance (BACS: treatment difference=1.31, 95% CI, -0.10 to 2.72) and in overall functioning (GAF: treatment difference=3.0, 95% CI, -0.4 to 6.4). Post hoc analysis of the individual cognitive domains showed that there was a significantly greater improvement in motor speed in the cannabidiol group relative to the placebo group ($p<0.05$), and a non-significantly greater improvement in executive functions ($p=0.068$). The other randomized controlled trial including 39 schizophrenia patients reported that cannabidiol treatment (600 mg/day) for 6 weeks did not affect cognitive functions (MCCB Composite score), and a post hoc analysis revealed that only placebo-treated subjects improved over time ($p=0.03$)[9].

Recreational drug users: MIXED. A 2017 review of 13 clinical studies evaluating the effects of THC versus cannabidiol on human cognition suggested that cannabidiol may improve cognition in cannabis users; some acute THC-induced cognitive impairments may be prevented if THC is administered in combination with cannabidiol [11]. In particular, memory components appear to be the cognitive domains more consistently disrupted following acute THC administration, including verbal, episodic, and

working memory. THC and cannabidiol appear to have antagonistic effects on neural networks underlying several cognitive processes, some of which correlate with the harmful (e.g., THC-induced psychotic or anxiety symptoms) or beneficial (e.g., anxiolytic effect of cannabidiol) effects of these cannabinoids on behavior.

Other studies have shown a lack of benefit. In an open-label clinical trial of 20 frequent cannabis users, cannabidiol treatment (200 mg/day) for 10 weeks did not result in significant effects on cognitive functions [12]. Participants reported significantly fewer depressive and psychotic-like symptoms at post-treatment relative to baseline, and exhibited improvements in attentional switching, verbal learning, and memory. Increased plasma cannabidiol concentrations were associated with improvements in attentional control and beneficial changes in psychological symptoms. While the general trends were positive, due to the lack of a placebo control, improvements seen post-treatment could be due to practice effect.

In a double-blind randomized controlled crossover trial of 43 polydrug (recreational) users, a single dose of cannabidiol (Epidiolex, 750, 1500, and 4500 mg) had no observable effect on cognitive and psychomotor tests [13].

Human research to suggest benefits to patients with dementia:

No studies have tested cannabidiol specifically in dementia patients. A randomized double-blind clinical trial showed that Nabilone, a synthetic cannabinoid, may be effective in treating agitation in people with Alzheimer's disease ([Press release from AAIC 2018](#)).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Neuroimaging: MINOR CHANGES IN VOLUME AND CONNECTIVITY. In an open-label MRI study in 18 cannabis users, cannabidiol treatment (200 mg/day) for 10 weeks did not significantly change volumes of the left or right hippocampus [14]. However, left subicular complex (parasubiculum, presubiculum, and subiculum) volume significantly increased from baseline to post-treatment ($p=0.017$ uncorrected) by 1.58% (Cohen's $d=0.63$; 2.83% in parasubiculum). Associations between greater right subicular complex and total hippocampal volume and higher plasma cannabidiol concentration were found, particularly in heavy users. It is worth noting that no adjustments were made for multiple comparisons, and given the number of regions assessed (14 areas x 2 to account for left and right), it is possible that the changes observed were due to chance.



In a functional MRI study in 16 healthy adults, a single dose of cannabidiol (600 mg) enhanced connectivity between the frontal cortex and the striatum (putamen)[15]. The behavioral correlate of this enhanced connectivity is unknown.

Preclinical data: IMPROVES COGNITIVE FUNCTIONS. Cannabidiol treatment prevents cognitive dysfunction in rodent models of Alzheimer's disease [16; 17; 18], Parkinson's disease [19], memory impairment (induced by iron)[20], and brain ischemic injury [21]. Mechanisms included increased neurogenesis [21], increased levels of the neurotrophic factor BDNF [21], decreased apoptotic proteins (caspase 9, APAF1, caspase 3)[22], and microglial migration [18]. In hippocampal slices exposed to A β 42, pretreatment with cannabidiol rescued the deficit in synaptic plasticity (as measured by long-term potentiation)[23]. This protection was mediated by PPAR γ , since a PPAR γ antagonist prevented this benefit. Stimulation of PPAR γ is thought to have anti-inflammatory action by inhibiting NF-kB. Other mechanisms of action include effects on signaling pathways such as mTOR, autophagy and GSK3 β , resulting in neuroprotection, decreased proinflammatory responses, and facilitation of neuroplastic events [2].

In a cell culture study using mesenchymal stem cells (MSCs) derived from gingiva, cannabidiol treatment led to the downregulation of GSK3 β (involved in tau phosphorylation) by promoting PI3K/Akt signaling [24].

Studies in preclinical models of Alzheimer's disease demonstrate the ability of cannabidiol to reduce reactive gliosis and neuroinflammation as well as to promote neurogenesis [25]. Other rodent studies have shown cognitive benefits with cannabidiol treatment [8].

Cannabidiol versus THC: A review that compared cannabidiol with THC stated that cannabidiol does not possess euphoric properties, and exerts antipsychotic, anxiolytic, anti-seizure, as well as anti-inflammatory properties [26]. THC elicits adverse psychological and physiological effects amongst users, while cannabidiol has unique pharmacologic, physiologic, and behavioral effects with possible effects on brain regions subserving anxiety, mood and sleep complaints.

A review of preclinical literature on the effects of cannabidiol in Alzheimer's models reported that cannabidiol can antagonize the psychoactive effects associated with THC and possibly mediate greater therapeutic benefits than either cannabinoid alone [25]. For example, THC-treated mice exhibit impaired object recognition/working memory, and when adolescent mice are chronically exposed, they have increased repetitive and compulsive-like behaviors [27]. All THC-induced behavioral abnormalities were

prevented by the coadministration of cannabidiol, whereas cannabidiol alone did not influence behavioral outcomes.

APOE4 interactions: Unknown.

Aging and related health concerns: Numerous preclinical studies exist for various indications, including protection from stroke, atherosclerosis, cancer, and neuropathy, but no evidence from high quality, well-designed clinical trials in humans exist thus far.

Types of evidence:

- 4 meta-analyses
- 3 randomized controlled trials that are not in the meta-analyses
- 1 open-label clinical study in cancer patients
- 1 case study of 4 Parkinson's patients
- Numerous laboratory studies

Atherosclerosis: POTENTIAL BENEFIT BASED ON PRECLINICAL EVIDENCE. A review on the effects of cannabidiol for stroke prevention suggested that cannabidiol exerts an indirect effect on immune cell function by inhibiting the degradation of circulating endocannabinoids, thus increasing the availability of CB2 receptors on neutrophils and macrophages in atherosclerotic plaques [1]. Cannabidiol increases levels of the anti-inflammatory endocannabinoid anandamide but not the proinflammatory 2-AG. This augmented “endocannabinoid tone” likely explains the finding of reduced IL-1 β , IL-2, IL-6, and TNF- α in experimental conditions. Cannabidiol also attenuates NF- κ B activation in human coronary artery endothelial cells, along with nitrotyrosine formation and expression of inducible nitric oxide synthase (iNOS) and adhesion molecules ICAM-1 and VCAM-1 [28]. No studies have validated these preclinical findings in a clinical setting.

Cancer: POTENTIAL BENEFIT. In an open-label study of cancer patients treated with pharmaceutical-grade cannabidiol (average dose of 10 mg, twice daily, 3 days on and 3 days off, for up to 4 years), clinical responses were seen in 92% of the 119 cases with solid tumors including a reduction in circulating tumor cells in many cases and in other cases, a reduction in tumor size, as shown by repeated scans [29]. The minimum duration of treatment required for cannabidiol was six months, but many continued for longer.



Several preclinical studies have shown potential benefits of cannabidiol for cancer. In a mouse model of pancreatic cancer (pancreatic ductal adenocarcinoma), cannabidiol treatment (100 mg/kg/day, i.p.) in addition to chemotherapy (gemcitabine, 100 mg/kg every 3 days) for up to 80 days significantly inhibited tumor cell proliferation and improved survival [30].

In 2 different breast cancer cell lines (ER-positive and triple-negative), cannabidiol inhibited cell survival and induced apoptosis in a dose dependent manner, based on morphological changes, DNA fragmentation, and an apoptosis assay [31]. Cannabidiol-induced apoptosis was accompanied by down-regulation of mTOR, cyclin D1 and up-regulation and localization of PPAR γ protein expression in the nuclei and cytoplasm.

A recent cell culture study showed that cannabidiol is a potent inhibitor of exosome and microvesicle release from three cancer cell lines: prostate cancer (PC3), hepatocellular carcinoma (HEPG2) and breast adenocarcinoma (MDA-MB-231)[32]. Cannabidiol did not affect cell viability after 1 hour of treatment. The exosome/microvesicle modulating effects of cannabidiol were dose dependent and cancer cell-type specific. This may be associated with changes in mitochondrial function, including modulation of STAT3 and prohibitin expression. The anti-cancer effects of cannabidiol may be partly due to the regulatory effects on exosome/microvesicle biogenesis. Exosome/microvesicle shedding from cancer cells aids active drug efflux and thus contributes to their resistance to chemotherapeutic agents.

Cardiovascular: LITTLE/NO EFFECT. A meta-analysis examining the hemodynamic effects of cannabidiol included 6 human studies and 19 studies in mammals [33]. None of the human studies that tested cannabidiol (Epidiolex[®], ranging from 100-1200 mg, or 10 mg/kg) showed significant changes in heart rate, systolic blood pressure, diastolic blood pressure, or heart rate. Changes were not observed with acute or chronic dosing. However, under a stressful situation (simulated public speaking test), acute cannabidiol administration significantly attenuated the increase in blood pressure and heart rate induced by stress (BP, mean difference (MD) -3.54; 95% CI, -5.19, -1.9; $p < 0.0001$; HR, MD -16.23; 95% CI, -26.44, -6.02; $p = 0.002$). In mouse models of stroke, cannabidiol significantly increased cerebral blood flow. Further studies are required to fully understand the potential hemodynamic effects of cannabidiol in humans under normal and pathological conditions.

In a small double-blind randomized controlled trial (crossover) of 9 healthy volunteers (not included in the above meta-analysis), a single dose of cannabidiol (600 mg) reduced resting systolic blood pressure (-6 mmHg; $P < 0.05$) and stroke volume (-8 ml; $P < 0.05$), with increased heart rate (+10 bpm; $P < 0.01$) and maintained cardiac output [34]. In response to cold stress, subjects who had taken cannabidiol had



blunted blood pressure (-6 mmHg; $P < 0.01$) and increased heart rate (+7 bpm; $P < 0.05$), with lower total peripheral resistance. Cannabidiol may cause sympathoinhibition (through CB1 or some other mechanism), thereby preventing an increase in blood pressure and cardiac output, causing a compensatory rise in heart rate to maintain cardiac output. Another possibility is that cannabidiol inhibits cardiac vagal tone, thereby increasing heart rate. A study in rats suggested a role of cannabidiol in the autonomic nervous system via weak partial agonist activity at GPR18 [35]. Further research is also required to establish whether cannabidiol has any role in the treatment of cardiovascular disorders such as hypertension.

Colitis/Crohn's disease: NO BENEFIT. A Cochrane meta-analysis of 2 randomized controlled trials in a total of 92 patients with ulcerative colitis reported that no firm conclusions regarding the efficacy of cannabidiol could be drawn [36]. One trial used cannabidiol (50-250 mg twice daily) with up to 4.7% THC (and the other trial used cannabis cigarettes). Clinical response at 10 weeks was achieved in 31% (9/29) of cannabidiol participants compared to 22% (7/31) of placebo patients (RR=1.37, 95% CI, 0.59 to 3.21). Serum CRP levels were not significantly different between cannabidiol and placebo groups after 10 weeks of therapy (9.428 mg/L in cannabidiol compared to 7.638 mg/L in the placebo group).

A different meta-analysis of 2 clinical studies (and 51 mouse studies) in colitis and Crohn's disease reported that cannabidiol is not effective in reducing disease severity (measured by disease activity index)[37]. However, the study in Crohn's disease only included 19 patients and the dose used (10 mg twice daily for 8 weeks) was very low [38]. It is not known if more commonly used doses (50-750 mg) would be effective. For reference, the dose typically used in children with epilepsy is 2.5-10 mg/kg, twice daily.

Lifespan: UNKNOWN. No studies have examined the effects of cannabidiol on lifespan or mortality in humans. In a rat model of sepsis (cecal ligation and puncture), cannabidiol treatment (2.5, 5, or 10 mg/kg daily for 9 days) reduced oxidative stress levels (TBARS and carbonyl levels) in some organs and significantly reduced mortality [39]. Untreated rats had 50% survival, while 10 mg dose had 90%, and 2.5 and 5 mg doses had around 70% survival across 10 days.

Neuropathy: UNKNOWN. A Cochrane meta-analysis including 16 studies with a total of 1,750 participants with chronic neuropathic pain reported that cannabis-based medicines may provide pain relief, though the difference between cannabis-based treatment and placebo groups appeared small (39% versus 33% of people achieving greater than 30% pain relief)[40]. Of the 16 studies, 10 studies used oromucosal spray including THC and cannabidiol (e.g., 48 sprays/day of 27 mg THC; 25 mg

cannabidiol, for 2-26 weeks). Because none of the studies looked at cannabidiol alone, it is not known if it may be beneficial in people with neuropathy.

In a mouse model of neuropathic pain (induced by paclitaxel), cannabidiol treatment (2.5-10 mg/kg on alternate days) prevented pain responses (mechanical sensitivity)[41]. This effect was mediated in part by the serotonin 1A (5HT-1A) receptor system (as the benefits disappeared when 5HT-1A antagonist was co-administered). Furthermore, cannabidiol treatment did not attenuate the chemotherapy's ability to inhibit breast cancer cell viability.

In a mouse model of sciatic nerve transection, cannabidiol injections for 5 days following injury resulted in a significant rescue of dorsal root ganglion neurons, spinal motoneurons, and pre-synaptic terminals, which was coupled with a reduction in neuronal apoptosis and astrogliosis [42]. Cannabidiol also suppresses astrocyte activity and proinflammatory signaling in astrocytes [43].

Inflammation: POTENTIAL BENEFIT BASED ON PRECLINICAL EVIDENCE. A 2011 review discusses cannabidiol as a promising therapeutic for reducing inflammation and oxidative stress [28]. Cannabidiol attenuates inflammation beyond its antioxidant properties, by targeting inflammation-related intracellular signaling events. For example, cannabidiol is a competitive inhibitor in the nanomolar range, of adenosine uptake by macrophages and microglial cells. By increasing exogenous adenosine, which in turn activates the A2A adenosine receptor, cannabidiol exerts immunosuppressive actions on macrophages and microglial cells as evidenced by decreased TNF α production.

Parkinson's disease: NO BENEFIT/POSSIBLE BENEFIT IN PATIENTS WITH ABNORMAL SLEEP BEHAVIOR. In a small double-blind randomized controlled trial of 21 Parkinson's disease patients (without dementia or psychiatric conditions), cannabidiol treatment (75 or 300 mg/day) for 6 weeks did not significantly improve motor symptoms, general symptoms, or plasma levels of the neurotrophic factor BDNF [44]. However, in a case report of 4 Parkinson's patients with abnormal sleep behavior, cannabidiol treatment (75 mg or 300 mg/day) for 6 weeks significantly reduced the frequency of REM sleep behavioral disorder-related events (from 2-7 times per week to 0 or 1 time per week)[45]. Upon drug discontinuation, these abnormal behavioral events returned with the same frequency and intensity. Mechanisms are not clearly known.

Stroke: POTENTIAL BENEFIT. No studies have examined the effects of cannabidiol in stroke patients. A meta-analysis of experimental stroke models including 34 studies (144 experiments testing various cannabinoids) reported that cannabidiol reduced infarct volume [46]. A dose response relationship was



observed with cannabidiol, with the greatest lesion volume reduction at 6 mg/kg (SMD – 1.89; 95% CI, –2.7 to –1.07; $P < 0.00001$, 6 studies, 57 animals). No effect was seen at a higher dose of 10 mg/kg (1 study, 9 animals). It is not clear if cannabidiol treatment is effective in humans or when given after stroke in experimental models.

Safety: Mild adverse events are common, including somnolence, decreased appetite, gastrointestinal issues, and increased liver enzymes. Some drug interactions are known (e.g., cilostazol, citalopram, clopidogrel, flibanserin).

Types of evidence:

- 3 meta-analyses
- 6 randomized controlled trials
- 2 open-label clinical trials
- Several laboratory studies

Long-term safety studies have not been carried out in healthy adults. Short-term safety data are available for patient populations described below.

Epilepsy patients: MILD ADVERSE EVENTS (e.g., SOMNOLENCE, INCREASED LIVER ENZYMES). The largest meta-analysis included 2 randomized controlled trials with a total of 396 epilepsy patients receiving cannabidiol as adjunctive treatment (5-20 mg/kg, twice daily) for 3-14 weeks [6]. Cannabidiol treatment was associated with an increased risk for experiencing adverse events than placebo (RR for any adverse event, 1.24; 95% CI, 1.11-1.38). Adverse events significantly associated with cannabidiol were somnolence, decreased appetite, diarrhea, and increased liver enzymes (serum aminotransferases). Adverse events were reported in 87.9% and 72.2% of the patients during treatment with cannabidiol and placebo, respectively (RR=1.22; 95% CI, 1.11–1.33). The treatment with cannabidiol was associated with a higher incidence of treatment-related adverse events (55.7% vs. 26.9%), severe adverse events (SAEs; 18.6% vs. 6.7%), and treatment-related SAEs (7.7% vs. 0.4%) in comparison to placebo. The incidence rates of adverse events that were significantly different between cannabidiol- versus placebo-treated participants were: somnolence, 24.5% versus 8.4%; decreased appetite, 20.1% versus 4.8%; diarrhea, 18.2% versus 8.6%; increased alanine or aspartate aminotransferases (more than 3 times the upper normal limit), 16.1% versus 0.9%; and sedation 9.7% versus 1.1% (*trend, $p=0.063$).



Cancer patients: NO ADVERSE EVENTS. In an open-label study of 119 cancer patients treated with pharmaceutical-grade cannabidiol (average dose of 10 mg, twice daily, 3 days on and 3 days off, for up to 4 years), no side effects were reported [29].

Schizophrenia patients: MILD ADVERSE EVENTS. In a double-blind randomized controlled trial of 88 schizophrenia patients, cannabidiol treatment (1000 mg/day for 6 weeks) was well-tolerated and rates of adverse events were similar between the cannabidiol and placebo groups [10]. There were 30 reported treatment-emergent adverse events in 15 patients in the cannabidiol group and 35 events in 16 patients in the placebo group. Gastrointestinal events were the most common and were reported by nine patients in the cannabidiol group and three in the placebo group. In both groups, most events (80% and 81%) were mild and resolved without intervention. Two patients in the cannabidiol group experienced a treatment-emergent adverse event that later resolved: mild lowered blood pressure and moderate chest pain; neither was considered treatment related. Ten treatment-emergent adverse events were still ongoing at the end of the trial, reported by three patients in the cannabidiol group and four in the placebo group. Only 2 events in the cannabidiol group were considered treatment-related (dyslipidemia and nausea); both were mild. The withdrawal from the cannabidiol group (n=1) was due to nausea, diarrhea, abdominal pain, and vomiting, and the withdrawal from the placebo group was due to somnolence and altered perception. In both cases, these symptoms subsequently resolved.

In a smaller randomized controlled trial in 39 schizophrenia patients, side effects were similar between cannabidiol (600 mg/day for 6 weeks) and placebo with one exception being sedation, which was more prevalent in the cannabidiol group [9]. Cannabidiol was well-tolerated with no worsening of mood, suicidality, or movement side effects.

Colitis/Crohn's disease patients: MILD ADVERSE EVENTS. A Cochrane meta-analysis of 2 randomized controlled trials including a total of 92 patients with ulcerative colitis examined the effects of cannabidiol; however, treatments for both studies included cannabinoids other than just cannabidiol (e.g., THC)[36]. The cannabidiol treatment consisted of 50-250 mg twice daily for 8-10 weeks. Adverse events were more frequent in cannabidiol participants compared to placebo. One hundred per cent (29/29) of cannabidiol participants had an adverse event, compared to 77% (24/31) of placebo participants (RR=1.28; 95% CI, 1.05 to 1.56). However, these adverse events were considered mild or moderate in severity. Common adverse events included dizziness, disturbance in attention, headache, nausea and fatigue. None (0/29) of the cannabidiol participants had a serious adverse event compared to 13% (4/31) of placebo participants. Serious adverse events in the placebo group included worsening



of ulcerative colitis and one complicated pregnancy. These serious adverse events were thought to be unrelated to the study drug. Withdrawals in the cannabidiol group were mostly due to dizziness.

In a small randomized clinical trial of 19 Crohn's disease patients, hemoglobin, albumin, and kidney and liver function tests remained unchanged with cannabidiol treatment (10 mg, twice daily for 8 weeks), and no side effects were significantly different between treatment and placebo [38].

Huntington's disease patients: NO SIGNIFICANT ADVERSE EVENTS. In a small double-blind randomized controlled trial of 15 Huntington's disease patients, cannabidiol treatment (10 mg/kg/day for 6 weeks) did not result in significantly greater numbers of side effects compared to placebo (477 in cannabidiol, 471 in placebo)[7]. There were no differences in blood pressure, pulse rate, or body weight. Abnormalities associated with cannabidiol were few and were mostly outside the normal ranges for the given tests, and authors considered these abnormalities to be random occurrences.

Recreational drug users: MILD ADVERSE EVENTS (e.g., INCREASED LIVER ENZYMES). In a double-blind randomized controlled crossover trial of 43 polydrug (recreational) users, a single dose of low-dose cannabidiol (Epidiolex[®], 750 mg) had low abuse potential [13]. Higher and supratherapeutic doses of cannabidiol (Epidiolex[®], 1500 mg and 4500 mg, respectively) had detectable subjective effects compared with placebo; however, the effects were significantly lower than those observed with alprazolam (i.e., Xanax) and dronabinol (synthetic form of Δ^9 -THC). There were no severe adverse events and all adverse events were moderate and mild in severity. Three subjects in the cannabidiol group discontinued study treatment: one (on 1500 mg dose) due to increased aspartate aminotransferase and blood creatine phosphokinase (AST increase was considered treatment-related), and two on 4500 mg dose due to ECG abnormality (prolonged QT interval) and hypersensitivity. Hypersensitivity was considered treatment related, but prolonged QT interval was considered unrelated to study treatment. Mean ECG parameters were within normal limits across the study, and no subjects who received cannabidiol had abnormal ECG parameters considered clinically significant. With cannabidiol doses 750 mg, 1500 mg, and 4500 mg, euphoric mood was reported in 2 (5.3%), 2 (5.1%), and 3 (7.5%) subjects, respectively. The incidence of somnolence with cannabidiol doses were 30.0% at the 4500 mg dose, 30.8% at the 1500 mg dose, 23.7% at the 750 mg dose, and 21.6% with placebo. Cannabidiol was not associated with changes in vital signs compared with placebo.

In an open-label clinical trial in 20 frequent cannabis users, cannabidiol (200 mg/day for 10 weeks) was well-tolerated with no reported side effects [12]. However, subjects retrospectively reported reduced euphoria when smoking cannabis.

Effects on sleep architecture in healthy adults: NO EFFECTS. In a small double-blind randomized controlled trial in 27 healthy adults, no differences were found between cannabidiol treatment (300 mg/day for 2 days) and placebo in respect to polysomnographic findings [4]. Unlike widely used anxiolytic and antidepressant drugs such as benzodiazepines and SSRIs, the acute administration of cannabidiol does not appear to interfere with the normal sleep architecture of healthy adults. No significant cannabidiol effects were seen on measures including sleep onset latency, REM onset latency, wake after sleep onset, sleep efficiency, % stage 1, % stage 2, % stage 3, and % REM.

Preclinical studies: POTENTIAL DNA-DAMAGING EFFECTS. In an *in vitro* study using human liver cell line (HepG2) and in buccal-derived cells (TR146), cannabidiol caused formation of comets (which reflect single and double strand breaks and apurinic sites), oxidation of DNA bases, and induction of micronuclei which are formed as a consequence of structural and numerical chromosomal aberrations [47]. The effects were seen at concentrations which are in the range of the levels also found in the blood of cannabis users. For reference, the highest concentrations of cannabidiol detected after smoking were between 0.25 and 2.18 μM in plasma. It is not clear if these DNA-damaging effects also occur *in vivo*, or if these effects may occur in specific cells such as cancer cells.

Drug interactions: Cannabidiol interacts with several drugs, notably valproate products, which may enhance the hepatotoxic effect of cannabidiol ([Drugs.com](https://www.drugs.com)). Cannabidiol is metabolized primarily by the liver by CYP2C19, CYP3A4, UGT1A7, UGT1A9, and UGT2B7 to the active metabolite 7-hydroxy-cannabidiol, and then to the inactive metabolite 7-COOH-cannabidiol ([Drugs.com](https://www.drugs.com)). Because of dose-related elevations of liver enzymes (ALT and/or AST), cannabidiol may interact with drugs metabolized by CYP2C19 (e.g., cilostazol, citalopram, clopidogrel, flibanserin) and CYP3A4 inhibitors/inducers. People with liver disease should use cannabidiol with extreme caution. Cannabidiol use in people with depression may make these conditions worse. High fat/high calorie meals increase the extent of absorption ([Drugs.com](https://www.drugs.com)).

Sources and dosing: Epidiolex[®] was approved by the FDA for two rare forms of childhood epilepsy—Lennox-Gastaut syndrome and Dravet syndrome. It is the first FDA-approved cannabidiol-based product available in the US. There are other cannabidiol-containing products on the market, but the main difference is that Epidiolex[®] contains only cannabidiol as an active ingredient, and its purity and manufacturing process have been approved by the FDA ([Cafepharm.com](https://www.cafepharm.com)). There are products labeled as “dietary supplements” on the market that contain cannabidiol, but the amount of cannabidiol contained is not always reported accurately on the product label ([WebMD.com](https://www.webmd.com)).



In seizure disorders, the initial dose is 2.5 mg/kg twice daily, taken orally, then may be increased after one week to a maintenance dose of 5 mg/kg twice daily ([Drugs.com](#)). If needed and tolerated, the dose may be further increased in weekly increments of 2.5 mg/kg twice daily to a maximum dosage of 10 mg/kg twice daily. When stopping to take cannabidiol, the dose needs to be decreased gradually before stopping completely.

Treato.com: Cannabidiol does not have a rating, but there are numerous discussions (over 20,000 as of 11/1/2018)([Treato.com](#)). Discussion topics include cannabidiol treatments for pain, anxiety, cancer, seizures, and epilepsy.

Research underway: There are numerous (50+) ongoing clinical trials testing cannabidiol ([ClinicalTrials.gov](#)). Patient populations include those with anxiety, PTSD, bipolar disorder, schizophrenia, epilepsy, substance abuse disorder (cannabis, alcohol, cocaine, etc.), Crohn's disease, irritable bowel syndrome, Parkinson's disease, heart failure, chronic pain, and other conditions.

Search terms:

Pubmed, Google: cannabidiol

- + meta-analysis, + Cochrane, + clinical trial, + cognitive, + Alzheimer's, + ApoE4, + lifespan, + mortality, + cancer, + cardiovascular, + atherosclerosis

Websites visited for cannabidiol, Epidiolex:

- [Clinicaltrials.gov](#)
- Examine.com (0)
- [Treato.com](#)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com ([cannabidiol](#), [epidiolex](#))
- [WebMD.com](#)
- [PubChem](#)
- [DrugBank.ca](#)
- Labdoor.com (0)
- [ConsumerLab.com](#)
- [Cafepharma](#)
- Pharmapro.com (0)



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