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

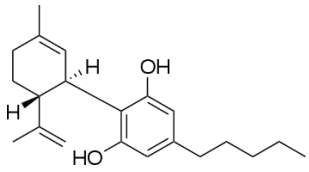
Evidence Summary

Cannabidiol has been tested in many trials, with mostly negative findings. In dementia patients, it may reduce agitation. Adverse events include GI issues, increased liver enzymes, and cognitive issues.

Neuroprotective Benefit: Cannabidiol treatment may reduce agitation in dementia patients, but no consistent benefits on cognitive function have been seen in other conditions including in healthy adults. Little data exist for long-term treatment.

Aging and related health concerns: While preclinical data appear promising for various indications, data from clinical trials in humans have been less compelling, with most studies showing a lack of benefit or the body of evidence is mixed.

Safety: Common adverse events include somnolence, decreased appetite, gastrointestinal issues, increased liver enzymes, drug-induced liver injury, and some cognitive issues. There are also drug-drug interactions.

Availability: Epidiolex®, available with prescription	**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)	**Chemical formula:** $C_{21}H_{30}O_2$ **MW**: 314.464 
Half life: 1-2 hours for elimination from plasma; terminal elimination half-life between 56-61 hours	**BBB**: penetrant	
Clinical trials: The largest meta-analysis of 12 randomized controlled trials included a total of 1,229 participants across various disease indications.	**Observational studies**: none that specifically examine cannabidiol	

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 also approved for treating seizures in people with tuberous sclerosis complex. People also take cannabidiol-containing products off-label for anxiety, pain, dystonia (a muscle disorder), multiple sclerosis, Parkinson's disease, Crohn's disease, and others (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 PPARγ 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 GSK3β, 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]. Δ9-tetrahydrocannabinol (THC) appears to be responsible for many of the negative effects, while cannabidiol has been shown to counteract some of these negative effects (e.g., anxiogenic effects).

Neuroprotective Benefit: Cannabidiol treatment may reduce agitation in dementia patients, but no consistent benefits on cognitive function have been seen in other conditions including in healthy adults. Little data exist for long-term treatment.

Types of evidence:

- 3 meta-analyses, 1 in epilepsy, 1 in schizophrenia, and 1 across different indications
- 12 randomized controlled trials
- 2 open-label clinical trials
- 2 neuroimaging studies in humans
- 1 case study in frontotemporal dementia
- Numerous laboratory studies
- Numerous review articles

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: MIXED FINDINGS ON COGNITION; MAY REDUCE ANXIETY AND INCREASE SEDATION
A 2024 meta-analysis of 16 randomized controlled trials (in adults with social anxiety, psychosis, nicotine dependence, schizotypy, chronic pain, and healthy adults), acute administration of cannabidiol resulted in a statistically significant, but a small effect size, impairment in cognitive performance compared to placebo (p=0.019)[4]. Cannabidiol treatment was associated with a small increase in self-reported (subjective feelings of) sedation/drowsiness. Cannabidiol treatment did not show significant differences compared to placebo in multiple domains of objectively assessed cognitive or psychomotor performance

(memory, psychomotor ability, driving performance, information processing, attention, or higher order cognitive functioning). Δ9-THC had a significantly greater magnitude of impairment compared to cannabidiol.

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)[5]. 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 [6]. 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.

In a double-blind randomized controlled trial of 34 healthy young people, a single vaping dose of cannabidiol e-liquid (0.25 ml containing 12.5 mg cannabidiol, 99% purity; vaping with Canna Vape kit) enhanced the primary outcome of episodic memory performance (measured by word free recall) compared to placebo ($p=0.048$)[7]. There were no effects of cannabidiol on secondary outcome measures of attention or working memory.

In a double-blind randomized controlled crossover trial of 31 healthy adults, an acute dose of cannabidiol (1 ml sublingual dose of CannEpil®, containing 100 mg cannabidiol and 5 mg Δ9- THC) increased errors on visuospatial working memory (measured by total errors in Spatial Span) and delayed pattern recognition (measured by correct latency in Pattern Recognition Memory) and decreased task efficiency (measured by the Efficiency Score) relative to placebo ($p<0.05$ for all)[8]. Subjective Contentedness and Amicability were also increased at around 2.5 hours post cannabidiol-dosing, relative to placebo ($p< 0.01$ and $p<0.05$, respectively). Plasma concentrations of cannabidiol, THC, and their metabolites were not significantly correlated with any observed alterations in cognitive function or subjective state. Because CannEpil® contained THC, the effects of cannabidiol alone cannot be teased apart.

In a double-blind randomized controlled crossover trial of 17 healthy adults, an acute dose of cannabidiol (15, 300, or 1,500 mg of cannabidiol in up to 15 mL of medium-chain triglyceride oil; GD Cann®–C; GD Pharma Pty Ltd, Norwood, South Australia, Australia) did not impair simulated driving performance in most doses/assessments compared to placebo, but some comparisons to placebo were inconclusive [9]. Simulated driving was measured using the standard deviation of lateral position (SDLP),

a well-established measure of vehicular control. It was assessed between ~45-75 and ~210-240 minutes post-treatment using a two-part scenario with 'standard' and 'car following' components. No dose of cannabidiol impaired cognition or induced feelings of intoxication. Cannabidiol was found to persist in plasma for prolonged periods of time (over 4 weeks with the 1500 mg dose).

Epilepsy patients: NO BENEFIT
A meta-analysis was carried out in patients with Lennox-Gastaut syndrome, a form of epilepsy [10]. 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.

In an open-label study of 38 children/teenagers with treatment-resistant epilepsy, cannabidiol treatment (Epidiolex®; GW Research Ltd.) for one year as an add-on treatment did not significantly change cognitive function, as measured by the NIH Toolbox Cognition Battery, in those participants who were able to complete the testing, but there was a nonsignificant trend toward improvement in some cognitive domains [11]. Many participants (n=24) were unable to complete the NIH Toolbox because of the magnitude of their cognitive impairment, and in these cases, the participant's caregiver was asked to complete the Adaptive Behavior Assessment System - Second Edition (ABAS-II) as a measure of functional adaptive skills. Cannabidiol treatment did not significantly change the ABAS-II after one year.

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 [12]. 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 [13]. 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 additional randomized controlled trials testing cannabidiol specifically in schizophrenia patients [14; 15]. 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)[15]. 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 ($p=0.03$)[14].

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 [16]. 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 [17]. 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 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 [18].

Human research to suggest benefits to patients with dementia:

As of December 2024, the safety and efficacy of cannabidiol in dementia patients remain unclear [19]. There have been numerous anecdotal accounts and several small, short-term studies, but data from long-term randomized double-blind placebo-controlled trials testing the effects of cannabidiol in Alzheimer's disease or other forms of dementia are currently lacking.

Dementia patients: DECREASED AGITATION
In a double-blind randomized controlled trial of 52 participants with a diagnosis of a major neurocognitive disorder and associated behavioral disturbances, cannabidiol treatment (295 mg cannabidiol and 12.5 mg THC per ml, titrated from 1 drop to up to 21 drops per administration, 3 times per day; Avidekel, Tikun-Olam Cannbit Pharmaceuticals, Israel) significantly reduced agitation [20]. Cannabidiol treatment increased the proportion of subjects who had a Cohen-Mansfield Agitation Inventory score reduction of ≥ 4 points at week 16 (24/40 [60.0%] and 6/20 [30.0%] for cannabidiol and placebo groups, respectively; p=0.03). There was also a statistically significant difference in the proportion of subjects who had a Cohen-Mansfield Agitation Inventory score reduction of ≥ 8 points at week 16 (20/40 [50%] and 3/20 [15%], respectively; p=0.011). The cannabidiol treatment compared to the placebo group significantly reduced agitation/aggression by 29.4% (p=0.01) and sleep disturbances by 22.5% (p=0.03). There were no significant effects on cognitive function as measured by the Mini-Mental State Exam. Because this intervention included THC, with 31% of patients in the cannabidiol group reaching the maximum allowed THC dose of 10.5 mg, the investigators could not rule out a direct effect of THC contributing to the decrease in agitation and other behavioral disturbances. Participants in the active and placebo groups consumed on average 14.9 and 17.9 drops per administration, respectively. The mean cannabidiol and THC consumption was 527.5 mg and 22.3 mg per day, respectively.

Alzheimer's disease patients: IMPROVED NEUROPSYCHIATRIC CONDITIONS
In a phase 2a double-blind randomized controlled trial of 15 Alzheimer's patients with behavioral and psychological symptoms, cannabidiol treatment (oral capsules of 200 mg, starting with one capsule daily and titrated upwards to 3 capsules daily) for 6 weeks improved the total score of Neuropsychiatric Inventory-clinician rating scale (cannabidiol, -29.86 ± 51.50; placebo, -10.14 ± 38.15), and hallucinations,

anxiety, agitation, apathy/indifference, and irritability/lability domains, along with caregiver distress compared to placebo [21]. The cannabidiol and placebo groups were mostly comparable in terms of baseline sociodemographic and clinical characteristics, except that the placebo group had more severe delusions and better quality of life at baseline. The final sample size was much smaller than originally planned due to the challenges posed by the COVID-19 pandemic.

Parkinson's disease patients: NO BENEFIT ON MOTOR FUNCTION
In a double-blind randomized controlled trial of 61 patients with Parkinson's disease, cannabis extract treatment (including both cannabidiol and THC at a dose of 2.5 mg/kg/day) for 2 weeks did not significantly affect motor function (measured by part III MDS-UPDRS) compared to placebo, with both groups showing improvements compared to baseline (with the cannabis group showing numerically greater improvement than placebo)[22]. Sleep, cognition, and activities of daily living showed a trend towards worsening with cannabis treatment compared to placebo. Because the intervention included both cannabidiol and THC, and the strong placebo response, it is not possible to tease apart the effects of cannabidiol alone.

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 [23]. 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)[24]. Upon drug discontinuation, these abnormal behavioral events returned with the same frequency and intensity. Mechanisms are not clearly known.

In a post hoc analysis of the randomized controlled trial described above, cannabidiol treatment (75-300 mg before bedtime; 99.6% pure powder in corn oil, BSPGPharm, UK) for 12 weeks did not reduce the severity of Restless Legs Syndrome/Willis-Ekbom Disease manifestation, the primary outcome, in 18 patients with Parkinson's disease and REM sleep behavior disorder [25]. There were also no treatment effects on secondary outcomes, including sleep satisfaction, night awakenings (based on sleep questionnaires) and objective sleep quality (measured by polysomnography).

Frontotemporal dementia patients: UNKNOWN
In a case study of one patient with awake bruxism (teeth grinding) and a behavioral variant of frontotemporal dementia, cannabidiol treatment (containing 4.8 mg cannabidiol and 0.31 mg of THC)

almost completely relieved bruxism [26]. This 52-year-old patient with a history of repetitive concussive head trauma episodes presented with psychiatric, behavioral, and cognitive changes, and teeth clenching that resulted in significant changes in his teeth alignment including an underbite. He received multiple treatments prior to cannabidiol (e.g., botulinum toxin A injections) with only a partial response. At the time of this publication, the patient's bruxism had remained under control for 6 months,. Patients with frontotemporal dementia have reduced presynaptic dopaminergic neurons and dopamine transporter binding, leading to abnormal dopamine binding in the nigrostriatal pathways [27]. Cannabidiol treatment may influence movement through the endocannabinoid system's interactions with the dopaminergic system.

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 [28]. 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 evident, 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 highly 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)[29]. 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 [30; 31; 32; 33], Parkinson's disease [34], memory impairment (induced by iron)[35], and brain ischemic injury [36]. Mechanisms included increased neurogenesis [36], increased levels of the neurotrophic factor BDNF [33; 36], increased synaptic proteins (e.g., GluA1, GluA2, synaptophysin, PSD95) [33], decreased apoptotic proteins (caspase 9, APAF1, caspase 3)[37], regulation of inflammatory markers (TNF-α and MCP-1) [33], and mitigation of microglial and astrocytic activation [32; 33]. In hippocampal slices exposed to Aβ42, pretreatment with cannabidiol rescued the deficit in synaptic plasticity (as measured by long-term potentiation)[38]. This protection was mediated by PPARγ, as an PPARγ antagonist

prevented this benefit. Stimulation of PPARγ 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 GSK3β, resulting in neuroprotection, decreased proinflammatory responses, and facilitation of neuroplastic events [2].

In a cell culture study using MSCs derived from gingiva, cannabidiol treatment led to the downregulation of GSK3β (involved in tau phosphorylation) by promoting PI3K/Akt signaling [39].

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 [40]. THC elicits adverse psychological and physiological effects amongst users, while cannabidiol has unique pharmacologic, physiologic, and behavioural 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 [41]. 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 [42]. 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: While preclinical data appear promising for various indications, data from clinical trials in humans have been less compelling, with most studies showing a lack of benefit or the body of evidence is mixed.

Types of evidence:

- 5 meta-analyses or systematic reviews
- 11 randomized controlled trials
- 2 open-label clinical studies
- 1 case study of 4 Parkinson's patients
- Numerous laboratory studies

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 [43]. Untreated rats had 50% survival, while those receiving a 10 mg dose had 90%, and 2.5 and 5 mg doses had around 70% survival across 10 days.

Physical fitness: NO BENEFIT
In a double-blind randomized controlled trial of 22 healthy adults, cannabidiol treatment (150 mg/day in MCT oil, 9 drops sublingually, daily) for 3 weeks did not improve performance in a 10-minute cycle ergometer trial compared to placebo [44]. There were no significant differences between cannabidiol or placebo groups for mean power during the 10-minute performance trial. There were also no significant differences in any of the physiological or perceptual parameters (heart rate, blood lactate, or ratings of perceived exertion) between cannabidiol and placebo groups.

In a double-blind randomized controlled trial of 48 healthy adults, cannabidiol treatment (50 mg/day; Six Degrees Wellness, Boulder, CO) for 8 weeks did not significantly alter body composition, aerobic fitness, muscular strength, physical activity, cognitive health, psychological wellbeing, and blood CRP concentrations [45]. The placebo group experienced a significant ~10% decrease in peak power while the cannabidiol group experienced a non-significant ~3% increase in peak power at the end of the intervention, though error bars were overlapping.

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-1β, IL-2, IL-6, and TNF-α in experimental conditions. Cannabidiol also attenuates NF-κB 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 [46]. No studies have validated these preclinical findings in a clinical setting.

Cardiovascular disease: MAY DECREASE BLOOD PRESSURE

A 2017 meta-analysis examining the hemodynamic effects of cannabidiol included 6 human studies and 19 studies in mammals [47]. 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 a double-blind randomized controlled crossover trial of 70 patients with hypertension, oral cannabidiol treatment (DehydraTECH2.0 CBD, 225-300 mg/day in first 2.5 weeks and 375-450 mg/day in the latter 2.5 weeks, taken 3 times a day) for 5 weeks significantly reduced average 24-hour mean, systolic, and diastolic blood pressure after 2.5 weeks (-3.22±0.90 mmHg, -4.76±1.24 mmHg, and -2.25±0.80 mmHg, respectively; $p<0.05$ for all)[48]. These values remained stable following the up-titration of cannabidiol for the remaining 2.5 weeks. Cannabidiol treatment did not significantly affect pulse wave velocity, a measure of arterial stiffness.

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 [49]. 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 [50]. Further research is also required to establish whether cannabidiol has any role in the treatment of cardiovascular disorders such as hypertension.

Stroke: POTENTIAL BENEFIT BASED ON ANIMAL MODELS

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 [51]. 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.

Cancer: MIXED FINDINGS
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 [52]. The minimum duration of treatment required for cannabidiol was six months, but many continued for longer.

In a phase 2b double-blind randomized controlled trial of 121 people with advanced cancer, cannabidiol oil treatment (100 mg/mL, titrated from 0.5 mL once daily to 2 mL 3 times a day) for 28 days did not significantly alter the total symptom distress score (TSDS) compared to a matching placebo [53]. Similarly, there was no detected difference in the proportion of responders. The median dose of participant-selected cannabidiol was 400 mg per day (range, 50-600). There was no detectable effect of cannabidiol treatment on quality of life, depression, or anxiety. Cannabidiol treatment did not add value to the reduction in symptom distress provided by specialist palliative care alone.

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 [54].

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 [55]. Cannabidiol-induced apoptosis was accompanied by down-regulation of mTOR, cyclin D1 and up-regulation and localization of PPARγ 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)[56]. 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 increases active drug efflux and thus contributes to their resistance to chemotherapeutic agents.

Neuropathy: UNCLEAR
A 2018 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)[57]. 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 pilot double-blind randomized controlled crossover study of 35 patients with chemotherapy-induced peripheral neuropathy, topical cannabidiol treatment (~4 mg twice daily; Nightingale Remedies, Portland, Oregon; pure cannabidiol with no other cannabinoids) for 2 weeks did not significantly alter neuropathy scores (measured by the EORTC-CIPN20) compared to placebo treatment [58].

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)[59]. 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 [60]. Cannabidiol also suppresses astrocyte activity and proinflammatory signaling in astrocytes [61].

Inflammation: POTENTIAL BENEFIT
A 2011 review discusses cannabidiol as a promising therapeutic for reducing inflammation and oxidative stress [46]. Cannabidiol attenuates inflammation far beyond its antioxidant properties, for example, 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 TNFα production.

UV-A radiation is associated with inflammation and oxidative damage. In a pilot double-blind randomized controlled trial of 19 healthy volunteers, nanoparticle-encapsulated cannabidiol cream or vehicle cream was applied to blinded buttock sites twice daily for 14 days, then the sites were irradiated with ≤3× UV-A minimal erythema dose [62]. Punch biopsies were taken after 24 hours for histology, immunohistochemistry, and gene expression studies. At 24 hours, 21% of participants had less observed erythema on cannabidiol-treated skin than on vehicle-treated skin. Cannabidiol-treated skin also had reduced UV-A-induced epidermal hyperplasia than vehicle-treated skin (p=0.01). Immunohistochemistry detected reduced oxidative damage (measured by cytoplasmic/nuclear 8-oxoguanine glycosylase 1 staining) in cannabidiol-treated skin compared with vehicle-treated skin (p<0.01). Quantitative mitochondrial DNA polymerase chain reaction demonstrated protection against mitochondrial DNA mutations associated with UV-A-induced skin aging (deletion of ND4 [proxy:4977 bp deletion; p=0.003] and ND1 [proxy:3895 bp deletion; p=0.002]) with cannabidiol treatment compared to placebo. This study was not designed to compare this cannabidiol treatment with the current standard-of-care for UV-A protection such as sunscreen.

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 [63]. 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)[64]. 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 [65]. 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.

Pain: UNCLEAR; BENEFIT MAY DEPEND ON TYPE/SOURCE OF PAIN
So far, the evidence for the effectiveness of cannabidiol in the treatment of lower back pain is lacking [66]. In a double-blind randomized placebo-controlled trial of 100 patients with acute lower back pain, cannabidiol treatment (400 mg) added to standard emergency department analgesic medication was not superior in alleviating pain compared to placebo and standard of care [67]. The addition of cannabidiol did not alter the length of hospital stay or oxycodone use compared to the addition of placebo.

In a double-blind randomized controlled trial of 60 patients with temporomandibular disorders who experience sleep bruxism and pain, intraoral cannabidiol gel application (5 [10 mg of cannabidiol per side, 20 mg daily] or 10% [20 mg of cannabidiol per side, 40 mg daily]) before bedtime significantly reduced pain [68]. The reduction in pain, as measured by the visual analogue scale (VAS), among patients using the 10% cannabidiol formulation was 57.4% ($p<0.05$; VAS from 6.0 to 2.0), accompanied by a decrease in surface electromyography (sEMG) activity by 42.1% ($p<0.05$). Patients randomized to the 5% cannabidiol formulation experienced a 40.8% reduction in pain ($p<0.05$; VAS from 6.0 to 3.5). Patients randomized to the 10% cannabidiol formulation also had significantly decreased sleep bruxism index (by 51%; $p<0.05$). In contrast, the placebo control group did not exhibit any differences in measures throughout the study (VAS from 6.0 to 5.5). The cannabidiol gel was formulated by mixing 100% cannabidiol in powder form with hydrogel (based on hydroxyethyl cellulose) and using paraffin oil as a levitating liquid. Paraffin oil was used to facilitate the grinding of the cannabidiol powder, mixed manually in a mortar, then the cannabidiol was blended with the hydrogel.

Osteoarthritis: INCONCLUSIVE
In a double-blind randomized controlled trial of 86 patients with painful chronic osteoarthritis of the knee, high-dose cannabidiol treatment (titrated up to 600 mg/day in the first week, taken 3 times a day with a meal) for 8 weeks while being on paracetamol (3 g/day) did not significantly reduce pain compared to placebo added to paracetamol [69]. In this trial, an add-on treatment with high-dose cannabidiol had no additional analgesic effect compared to paracetamol alone.

In an open-label study of 15 patients with hand osteoarthritis, application of a novel transdermal cannabidiol gel (4% w/w, ~30 mg/day, 3 times per day; compounded by pharmacy in Victoria, Australia) for 4 weeks significantly reduced pain ratings (current pain, average pain, and maximum pain; $p<0.0001$ for all) over time compared to pre-treatment baseline [70]. A significant increase in grip strength in the treated hand was observed ($p<0.0001$), but self-reported hand functionality did not improve. Three quality of life measures were significantly improved with cannabidiol treatment: fatigue ($p=0.014$),

stiffness (p=0.004), and anxiety (p<0.0001). During the washout phase, the reductions in pain scores and increases in grip strength seen during the treatment reverted back towards baseline. Because this study was an open-label study, further confirmation in a placebo-controlled randomized trial is required. The transdermal cannabidiol gel contained tocopheryl phosphate mixture that is used as a transdermal permeation enhancer [71]. The tocopheryl phosphate mixture self-assembles into nanostructures to form elastic vesicles that encapsulate lipophilic molecules to increase their solubility in aqueous environments. This mixture has increased dermal absorption of various drug molecules. Systemic absorption of the cannabidiol gel was confirmed by the presence of cannabidiol and its metabolites in urine samples [70].

Safety: Common adverse events include somnolence, decreased appetite, gastrointestinal issues, increased liver enzymes, drug-induced liver injury, and some cognitive issues. There are also drug-drug interactions.

Types of evidence:

- 7 meta-analyses and systematic reviews
- 16 randomized controlled trials
- 3 open-label clinical trials
- 1 case study
- Several laboratory studies

There have been numerous meta-analyses and systematic reviews that have investigated the safety profile of cannabidiol treatment.

In a 2023 meta-analysis of 12 randomized controlled trials that included a total of 1,229 participants with various conditions (e.g., epilepsy, inflammatory bowel disease, Parkinson's disease, Fragile X disease), cannabidiol treatment for up to 6 months was associated with an increased probability of liver enzyme elevation compared to placebo controls (OR=5.85, 95% CI, 3.84 to 8.92) and drug-induced liver injury (OR=4.82, 95% CI, 2.46 to 9.45)[72]. Most cases of liver enzyme elevation were transient, with 80.5% reported as resolved. Of the resolved cases, 50.0% resolved following cessation of cannabidiol use, 25.0% resolved spontaneously with continued cannabidiol use, 16.4% resolved with a dose reduction of other antiepileptic medications, 1.6% resolved with dose reduction of cannabidiol, and 7.0% resolved with unclear reasons. Among drug-induced liver injury cases, 89.5% were resolved after the discontinuation of cannabidiol and 3.5% were reported as unresolved at the time monitoring ended.

High-dose cannabidiol (≥1000 mg/day or ≥20 mg/kg/day) and concomitant antiepileptic drug use (valproic acid) were identified as risk factors for both liver enzyme elevation and drug-induced liver injury. No cases of drug-induced liver injury were reported in adults taking cannabidiol doses under 300 mg/day. There were no cases of severe drug-induced liver injury, as determined by Hy's law. The proportion of cannabidiol-associated drug-induced liver injury is similar or greater to those found in other common hepatotoxic drugs such as statins (atorvastatin 1-3%, fluvastatin 1-5%, pravastatin 3-7%) and fluoroquinolones (1-3%) while being slightly lower than valproic acid (5-10%). Clinicians are encouraged to monitor liver enzymes in patients taking cannabidiol who have risk factors for liver dysfunction, taking moderate-to-high doses of cannabidiol (>300 mg/day), or using cannabidiol with antiepileptic medications. Serum liver enzymes are recommended to be assessed at baseline, 1, 3, and 6 months after cannabidiol initiation. If liver enzyme elevations are sustained, the cannabidiol dosage should be reduced or concomitant drugs should be adjusted. Cannabidiol should be discontinued in any patient with drug-induced liver injury.

The pathophysiology of liver injury associated with cannabinoid treatment is unclear, but some of these adverse events are likely related to other medications the patients are taking that have drug-drug interactions. Preclinical evidence suggests that high-dose cannabidiol can induce gene expression patterns associated with increased oxidative stress, which in turn may contribute to liver injury [73]. There may also be genetic differences in risk of liver enzyme elevation with cannabidiol. A pharmacogenetic study reported that in people with treatment-resistant epilepsy, the genetic variant ABCC5 rs3749442 was associated with a lower likelihood of abnormal liver function tests with cannabidiol treatment [74].

In a 2020 meta-analysis of 12 double-blind randomized controlled trials including a total of 803 participants, cannabidiol treatment (200 to 3,000 mg/day; mean dose of 1,132 mg/day) for 1-14 weeks resulted in an increased likelihood of withdrawal for any reason (OR=2.61) or due to adverse events (OR=2.65), any serious adverse event (OR=2.30), serious adverse events related to abnormal liver function tests (>3 times the upper limit of normal; OR=11.19) or pneumonia (OR=5.37), any adverse event (OR=1.55), adverse events due to decreased appetite (OR=3.56), diarrhea (OR=2.61), somnolence (OR=2.23) and sedation (OR=4.21) [75]. However, the associations with abnormal liver function tests, somnolence, sedation and pneumonia were limited to childhood epilepsy studies, where cannabidiol may have interacted with other antiepileptic medications. After excluding childhood epilepsy trials, the only adverse event associated with cannabidiol treatment was diarrhea (OR=5.03, 95% CI, 1.44 to 17.61).

Healthy adults: FEW ADVERSE EVENTS
In a double-blind randomized controlled trial of 48 healthy adults, cannabidiol treatment (50 mg/day; Six Degrees Wellness, Boulder, CO) for 8 weeks did not result in any severe adverse events or reports of supplement intolerance [45].

In a double-blind randomized controlled crossover trial of 17 healthy adults, an acute dose of cannabidiol (15, 300, or 1,500 mg of cannabidiol in up to 15 mL of medium-chain triglyceride oil; GD Cann®–C; GD Pharma Pty Ltd, Norwood, South Australia, Australia) did not result in any serious adverse events [9]. Adverse events from the study included one case of fainting from a baseline blood draw, and one case of nausea and vomiting from the driving test.

Epilepsy patients: SOMNOLENCE, INCREASED LIVER ENZYMES, AND OTHER ADVERSE EVENTS
A 2018 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 [10]. 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 to 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 to 1.33). The treatment with cannabidiol was associated with a higher incidence of treatment-related AEs (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 as follows: 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).

In a 2023 meta-analysis of 9 randomized controlled trials in epilepsy patients, cannabidiol treatment (ranging from 2.6 to 50 mg/kg, with most studies testing 20 mg/kg) for 3 to 16 weeks resulted in an overall adverse event incidence of 9.7% compared with 4.0% in the control group [76]. The overall risk ratios for any grade and severe grade adverse events were 1.12 (95% CI, 1.02-1.23) and 3.39 (95% CI, 1.42-8.09), respectively, for the cannabidiol group compared with the control group. Compared with the control group, the cannabidiol group had a greater risk for incidence of serious adverse events (RR=2.67; 95% CI, 1.83-3.88), adverse events resulting in discontinuation (RR=3.95; 95% CI, 1.86-8.37), and adverse events resulting in dose reduction (RR=9.87; 95% CI, 5.34-14.40). In cannabidiol-treated patients, the

most common adverse event was somnolence (22.0%), followed by decreased appetite (19.5%) and pyrexia (15.3%). In the controls, upper respiratory tract infection (11.8%), diarrhea (10.9%), and pyrexia (10.2%) were the most common adverse events. Incidences of diarrhea (RR=1.93; 95% CI, 1.44-2.58), somnolence (RR=2.29; 95% CI, 1.61-3.25), decreased appetite (RR=2.13; 95% CI, 1.48-3.06), and alanine transaminase (ALT) or aspartate aminotransferase (AST) elevation (RR=12.29; 95% CI, 4.22-35.80) were significantly higher in the cannabidiol group compared to control. The percentage of adverse events that led to the discontinuation of the trial was higher in the cannabidiol arm than in the controls (2.4% vs 0.7%). Most participants of this meta-analysis were treatment-resistant patients with epilepsy, but there was heterogeneity in the study in terms of age, disease severity, cannabidiol dosage/source, and route of administration. The use of other antiepileptic drugs can also influence the rate and type of adverse events.

Hypertension: MILD ADVERSE EVENTS
In a double-blind randomized controlled crossover trial of 70 patients with hypertension, oral cannabidiol treatment (DehydraTECH2.0 CBD, 225-300 mg/day in first 2.5 weeks and 375-450 mg/day in the latter 2.5 weeks, taken 3 times a day) for 5 weeks resulted in 8 mild adverse events, only during the first and second dosing periods [48]. Diarrhea was the most common adverse event with cannabidiol treatment (4.3% vs 0% during placebo trial). In the placebo trial, there were 6 reports of adverse events. Bloating, headache, and hypersomnia were equally distributed between cannabidiol and placebo trials. No serious adverse events were reported, and no participant discontinued treatment due to an adverse event. No participants had clinically relevant elevations in liver enzymes (AST, ALT, or TBL).

Dementia patients: MILD ADVERSE EVENTS; CONFUSION, MEMORY ISSUES, AND SLEEPINESS
In a double-blind randomized controlled trial of 52 participants with a diagnosis of a major neurocognitive disorder and associated behavioral disturbances, cannabidiol treatment (295 mg cannabidiol and 12.5 mg THC per ml, titrated from 1 drop to up to 21 drops per administration, 3 times per day; Avidekel, Tikun-Olam Cannbit Pharmaceuticals, Israel) was mostly safe with no significant differences in the occurrence of adverse events compared to placebo [20]. Sleepiness (48.6%), confusion and disorientation (45.9%), and decreased memory (32.4%) were the most frequent complaints among participants in the cannabidiol treatment group. Cannabidiol treatment showed trends for higher rates of decreased memory (p=0.06), hallucinations (p=0.08), sleepiness (p=0.17), and disorientation (p=0.18). However, there were no statistically significant differences in the occurrence of adverse events between cannabidiol and placebo groups. There were no significant changes in pulse or blood pressure throughout the study. Thirteen serious adverse events included 2 deaths (both in cannabidiol group) and 11 hospitalizations. The two deaths were not related to the intervention: the first patient, 94 years old,

suffering from colonic cancer and chronic renal failure died from septic shock, and the second patient, 87 years old, was recurrently hospitalized and intubated for severe hyponatremia and anemia and died from breathing difficulties. There were no significant differences in the occurrence of serious adverse events between cannabidiol and placebo groups (9 and 4 in the cannabidiol and placebo groups, respectively). Attrition for 6 patients was due to personal and caregiver difficulties. All withdrawals were in the cannabidiol group.

In a phase 2a double-blind randomized controlled trial of 15 Alzheimer's patients with behavioral and psychological symptoms, cannabidiol treatment (oral capsules of 200 mg, starting with one capsule daily and titrated upwards to 3 capsules daily) for 6 weeks had an adherence rate of 100% and retention rate of 94% [21]. A total of 34 adverse events were observed during the entire period of the study, with the most common being dizziness (cannabidiol, 63%; placebo, 0%); and falls (cannabidiol, 25%; placebo, 43%). There were no withdrawals or deaths in either group. There was one serious adverse event of a fall experienced by a participant in the placebo group after the end of the treatment.

Parkinson's patients: MOSTLY MILD ADVERSE EVENTS; SOME COGNITIVE ADVERSE EVENTS
In a double-blind randomized controlled trial of 61 patients with Parkinson's disease, cannabis extract treatment (including both cannabidiol and THC at a dose of 2.5 mg/kg/day) for 2 weeks resulted in mostly mild adverse events which were reported twice as many with the cannabidiol/THC treatment than placebo [22]. Adverse events occurred with the initial rather than the final dose. For example, dizziness, the most common adverse event in the cannabidiol/THC group, was rated as mild for 88.9% of the reports. Cognitive adverse effects were reported more frequently by the cannabidiol/THC group. Pneumonia was the only serious adverse event observed and occurred in one participant 10 days after they completed the study drug treatment. There were no effects on orthostatic blood pressure, heart rate, or temperature, comparing before the first study medication dose to the final dose, and comparing before a dose to 1 and 3 hours afterward. There were no notable changes in blood laboratory studies including liver function tests. Thirteen participants, all in the cannabidiol/THC group, did not reach the per protocol dose, including 7 for the 1.25 mg/kg/day visit and 6 for the 2.5 mg/kg/day visit, due to intolerance. One participant in the cannabidiol/THC group dropped out of the study due to adverse events after the first dose.

In a phase 2b double-blind randomized controlled trial of 58 patients with Parkinson's-related motor symptoms, an oral cannabidiol (100 mg) and low-dose THC (3.3 mg) treatment for ~16 days significantly worsened verbal fluency compared to the placebo group [77]. Adverse cognitive events were reported at least twice as often by the cannabidiol/THC-treated group than the placebo group, including dizziness

(58.1% vs. 20.0%), decreased concentration (32.3% vs. 13.3%), confusion (16.1% vs. 3.3%), feeling abnormal (25.8% vs. 6.7%), feeling drunk (22.6% vs. 6.7%), increased concentration (12.9% vs. 3.3%), disorientation (12.9% vs. 0%), and thinking abnormally (16.1% vs. 0%). Testing was performed 1-1.5 hours after cannabidiol/THC administration.

In a phase 1b double-blind randomized controlled trial of 8 patients with Parkinson's disease and pain, a cannabinoid/THC treatment of various formulations (20:1, 10:10, and 0:18 ratio; once per day, orally, in response to pain or at least 4 hours before bedtime) for 35 days resulted in the maximum tolerated dose that was similar across formulations [78]. The mean maximum tolerated doses were numerically similar across the three groups: 0.8 ml/day with 10:10 formulation (7.84 mg of THC and 7.92 mg of cannabidiol), 0.9 ml/day for 18:0 (17.01 mg of THC and 0.18 mg of cannabidiol), and 0.9 ml/day for 1:20 (0.9 mg of THC and 18 mg of cannabidiol). There were no serious adverse events or study dropouts. The most common adverse events were drowsiness and dizziness (3 participants). Epworth sleepiness scale scores were higher in the high cannabidiol formulation (1:20).

Huntington's disease patients: ADVERSE EVENTS SIMILAR TO PLACEBO
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)[12]. 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.

Schizophrenia patients: ADVERSE EVENTS SIMILAR TO PLACEBO
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 [15]. 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) followed 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 [14]. Cannabidiol was well-tolerated with no worsening of mood, suicidality, or movement side effects.

Osteoarthritis: MILD LIVER ENZYME ELEVATIONS, GI SYMPTOMS
In a double-blind randomized controlled trial of 86 patients with painful chronic osteoarthritis of the knee, high-dose cannabidiol treatment (titrated up to 600 mg/day in the first week, taken 3 times a day with a meal) for 8 weeks while being on paracetamol (3 g/day) was associated with frequent adverse events including diarrhea, abdominal pain, fatigue, and liver enzyme elevations [69]. Adverse events were very common in both groups, 93% in the cannabidiol arm experienced at least one adverse event and 88% reported at least one adverse event in the placebo group. Rise above baseline of liver enzymes (AST, ALT, and gamma-glutamyltransferase) was significantly more common in the cannabidiol (n=15) than the placebo group (n=5)(p=0.02). Many of these enzyme elevations were mild and clinically irrelevant. At the follow-up visit 4 weeks after cessation of cannabidiol/placebo, all liver enzyme elevations had fully resolved.

In an open-label study of 15 patients with hand osteoarthritis, application of a novel transdermal cannabidiol gel (4% w/w, ~30 mg/day, 3 times per day; compounded by pharmacy in Victoria, Australia) for 4 weeks led to 31 mild adverse events including headache (n=6), back pain (n=4), neck pain (n=3), shoulder pain (n=3), reflux (n=3), allergy (n=3), pain (n=2), inability to sleep (n=2), gastritis (n=1), cramps (n=1), body pain (n=2), and inflammation (n=1)[70]. Most of these adverse events resolved within the day.

Cancer patients: ADVERSE EVENTS SIMILAR TO PLACEBO EXCEPT DYSPNEA
In a phase 2b double-blind randomized controlled trial of 121 people with advanced cancer, cannabidiol oil treatment (100 mg/mL, titrated from 0.5 mL once daily to 2 mL 3 times a day) for 28 days resulted in adverse events that were not significantly different from placebo except for dyspnea, which was more common with cannabidiol treatment (8 in cannabidiol and 2 in placebo)[53]. The 10 most frequent categories of adverse events were pain, dyspnea, constipation, fatigue, anxiety, insomnia, peripheral neuropathy, diarrhea, anorexia, and edema. There were 8 serious adverse events resulting in

hospitalizations (5 in cannabidiol and 3 in placebo), but none were considered related to the study drug by the Data and Safety Monitoring Committee. There was no statistically significant difference in survival between groups (median, 95% survival 278 days [range, 160-426] in cannabidiol and 190 days [range, 137-317] in placebo).

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 [52].

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)[63]. 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 to1.56). 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 [65].

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 [18]. 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 [17]. 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 [5]. 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.

Cannabidiol products/supplements: LABELS CAN BE INACCURATE
Products labeled as "cannabidiol supplements" on the market do not always report the amount of cannabidiol accurately on the product label (WebMD.com). In the US marketplace, fewer than half of products surveyed contained cannabidiol concentrations within 20% of the amount noted on the label [79]. THC can also be found in some of these products at levels above what is noted on the label (but usually at levels below those used recreationally, e.g., up to 3 mg/serving).

In a case study, a 94-year-old woman was admitted with altered mental status, diarrhea, and hallucinations [80]. In the emergency room, her vital signs showed mild tachycardia and hypotension. She was lethargic, disoriented, confused, and anxious. After 5 days of admission, a close relative confessed that they had given the patient a cannabis product marketed as "pure cannabidiol" in the form of edible brownies to help her with her back pain (due to osteoporosis and arthritis) and poor

appetite. The urine test confirmed THC ingestion. A CT scan of her head showed moderate chronic ischemic microvascular disease with mild dilatation of ventricles, possibly reflecting mild hydrocephalus; the chronic white matter disease was appropriate for her age. Her diagnosis was cannabis-induced acute encephalopathy. She returned to her baseline level of cognitive function at the time of discharge. The cannabis-induced intoxication was likely due to her dehydration and poor oral intake prior to ingestion of the THC-containing brownies. This led to delirium and diarrhea, which in turn caused hypotension, acute kidney injury, and mild elevation of liver function tests. IV hydration improved the hypotension, hyponatremia, and kidney injury.

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 [81]. 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). 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). 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).

Sources and dosing:

Epidiolex® was approved by the FDA for two rare forms of childhood epilepsy—Lennox-Gastaut syndrome and Dravet syndrome. It was 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 (Cafepharma.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).

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 cannabidiol, the dose needs to be decreased gradually before stopping completely.

Research underway:

There are 160+ ongoing clinical trials testing cannabidiol (ClinicalTrials.gov). Patient populations include those with epilepsy, anxiety, PTSD, bipolar disorder, schizophrenia, substance abuse disorder (cannabis, alcohol, cocaine, etc.), insomnia, Crohn disease, irritable bowel syndrome, Alzheimer's disease, Parkinson's disease, Fragile X syndrome, spinal cord injury-induced neuropathy, chronic pain, post-operative pain, carpal tunnel syndrome, cancer, heart failure, liver injury, and other conditions.

A double-blind randomized controlled trial is testing the effects of cannabidiol treatment (200 mg/day for 6 months) in 236 people at risk for Alzheimer's disease on validated biomarkers of Alzheimer's disease progression, and cognitive and clinical measures (NCT05822362). The primary outcome is neurocognitive function, measured by CDR-SB, NIH-Toolbox cognitive battery, Rey auditory verbal learning test, MOCA, and functional activities questionnaire. Primary biomarker outcomes include plasma ptau-181, Aβ42/Aβ40 ratio, and neurofilament light. This study is scheduled to be completed in April 2029.

A double-blind placebo-controlled phase 2/3 study named MyC4D is testing the therapeutic benefits of cannabidiol treatment (dosing will range between 200 mg to 400 mg, administered twice daily) in 486 dementia patients in Malaysia (NCT06514066). Primary outcomes include cognitive, neuropsychological, and other measures (ADAS-Cog, Neuropsychiatric Inventory, Pittsburgh Sleep Quality Index, and QOL-AD Questionnaire). This study is scheduled to be completed in October 2025.

An open-label, 8-week clinical study is testing whether high cannabidiol, low THC sublingual solution reduces anxiety and agitation in 12 people with mild cognitive impairment or mild to moderate

Alzheimer's disease patients (NCT04075435). The primary outcome is the "total of clinical impression column on anxiety domain of the NPI-C). This study is scheduled to be completed in July 2025.

A double-blind randomized placebo-controlled phase 2 trial is evaluating the safety and tolerability of cannabidiol (Kanbis®; 100 mg, 300 mg, or 400 mg/ml) for the treatment of Parkinson's disease symptoms in 88 patients (NCT06629389). The primary outcome is the number of patients with adverse events related to treatment. This study is scheduled to be completed in November 2026.

A double-blind randomized placebo-controlled trial will test whether cannabidiol (titrated from 2.5 to 10 mg/kg, taken twice daily; Epidiolex, Greenwich Biosciences Inc.) exerts anti-neuroinflammatory effects in 80 people with chronic low back pain with or without mild-to-moderate depression (NCT05066308). The primary outcome is changes in neuroinflammation in the thalamus (measured by brain [11C]PBR28 signal). This study is scheduled to be completed in July 2025.

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)
- 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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