results on liver-function tests. Adverse effects led to the withdrawal of eight patients in the cannabidiol group compared with one in the placebo group.[65]

It has been suggested that some of the adverse effects of cannabidiol observed in the clinical studies may relate to interactions with other antiepileptic drugs. For example, a recent study evaluated thirteen subjects with refractory epilepsy concomitantly taking clobazam and CBD. Nine of 13 subjects had a >50% decrease in seizures, corresponding to a responder rate of 70%. Side effects were reported in 10 (77%) of the 13 subjects, but were alleviated with clobazam dose reduction. All subjects tolerated CBD well. [66]

It has been suggested that cannabidiol (as Epidiolex) is likely to be submitted for regulatory approval by GW Pharmaceuticals for epilepsy treatment in 2017 following the successful outcomes reported in treatment of Dravet syndrome.

Other indications

There is also evidence that CBD may be a useful treatment for a number of other medical conditions. However, this research is considerably less advanced than for treatment of epilepsy. For most indications, there is only pre-clinical evidence, while for some there is a combination of pre-clinical and limited clinical evidence. The range of conditions for which CBD has been assessed is diverse, consistent with its neuroprotective, antiepileptic, hypoxia-ischemia, anxiolytic, antipsychotic, analgesic, anti-inflammatory, anti-asthmatic, and antitumor properties.[37, 50, 67] The evidence for CBD's various therapeutic applications was recently reviewed by Pisanti et al (2017), refer to Table 1.

Another possible therapeutic application which has been investigated is the use of CBD to treat drug addiction. A recent systematic review concluded that there were a limited number of preclinical studies which suggest that CBD may have therapeutic properties on opioid, cocaine, and psychostimulant addiction, and some preliminary data suggest that it may be beneficial in cannabis and tobacco addiction in humans. However, considerably more research is required to evaluate CBD as a potential treatment. [68]

Table 1. Overview of diseases for which CBD may have therapeutic benefits taken from Pisanti et al (2017) [69]

Disease	Effects
Alzheimer's disease	Antinflammatory, antioxidant, antiapoptotic in *in vitro* and *in vivo* models of Aβ-evoked neuroinflammatory and neurodegenerative responses.
Parkinson's disease	Attenuation of the dopaminergic impairment *in vivo*; neuroprotection; improvement of psychiatric rating and reduction of agitation, nightmare and aggressive behaviour in patients.
Multiple sclerosis	Improved signs of EAE in mice, antinflammatory and immunomodulatory properties.
Huntington's disease	Neuroprotective and antioxidant in mice transgenic models; no significant clinically important differences in patients.
Hypoxia-ischemia injury	Short term neuroprotective effects; inhibition of excitotoxicity, oxidative stress and inflammation *in vitro* and in rodent models.
Pain	Analgesic effect in patients with neuropathic pain resistant to other treatments.
Psychosis	Attenuation of the behavioural and glial changes in animal models of schizophrenia; anti-psychotic properties on ketamine-induced symptoms
Anxiety	Reduction of muscular tension, restlessness, fatigue, problems in concentration, improvement of social interactions in rodent models of anxiety and stress; reduced social anxiety in patients.
Depression	Anti-depressant effect in genetic rodent model of depression.
Cancer	Antiproliferative and anti-invasive actions in a large range of cancer types; induction of autophagy-mediated cancer cell death; chemopreventive effects.
Nausea	Suppression of nausea and conditioned gaping in rats
Inflammatory diseases	Antinflammatory properties in several in vitro and in vivo models; inhibition of inflammatory cytokines and pathways.
Rheumatoid arthritis	Inhibition of TNF-α in an animal model
Infection	Activity against methicillin-resistant *Staphylococcus aureus*
Inflammatory bowel and Crohn's diseases	Inhibition of macrophage recruitment and TNF-α secretion *in vivo* and *ex vivo*; reduction in disease activity index in Crohn's patients.
Cardiovascular diseases	Reduced infarct size through anti-oxidant and anti-inflammatory properties *in vitro* and *in vivo*.
Diabetic complications	Attenuation of fibrosis and myocardial dysfunction

improvement. No improvements were observed in the placebo group and no toxic effects were reported for either group. This study has a number of limitations, including the small sample size, unclear design as to blinding, and lack of definition of partial improvement. [60]

In another study, 15 patients with "secondarily generalized epilepsy with temporal focus," were randomly divided into two groups. In a double-blind procedure, each patient received 200-300 mg daily of CBD or placebo for up to four and a half months in combination with their existing prescribed antiepileptic medications (which were no longer effective in the control of their symptoms). CBD was tolerated in all patients, with no signs of toxicity or serious side effects. Of the eight participants in the CBD treatment group, four were reported to be almost free of seizure episodes throughout the trial, whereas three others showed partial clinical improvement. CBD was ineffective in one patient. In comparison, the clinical condition of seven placebo patients remained unchanged with one patient showing improvement.[61]

There have also been some negative reports regarding the effectiveness of CBD. In a trial reported in 1986, a dose of CBD of 200–300 mg/day for a month resulted in no significant differences between the treatment and placebo groups. [62] Similarly, a 6-month double blind study administering CBD 100 mg 3 times each day did not result in any changes in seizure frequency or improvement in cognition or behaviour. [63]

The results of two trials examining the effects of CBD in patients with severe, intractable, childhood-onset, treatment-resistant epilepsy have been reported. The first was an open label study of 214 patients (aged 1–30 years) who were receiving stable doses of antiepileptic drugs before study entry. Patients were given oral cannabidiol, initially at 2–5 mg/kg per day, and then titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day, dependent on study site. The primary measure was the percentage change in the frequency of seizures. In the CBD group, the median monthly frequency of motor seizures reduced from 30·0 at baseline to 15·8 over the 12 week treatment period. The trial was also designed to assess safety, but the absence of a control group means that the results cannot be used to assess the likelihood of CBD producing particular effects. Adverse events reported in more than 10% of patients were somnolence, decreased appetite, diarrhoea, fatigue, and convulsion. Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, of which 20 (12%) experienced severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]). [64]

The same research group recently reported the results of a controlled trial of CBD treatment for Dravet syndrome, a complex childhood epilepsy disorder that is associated with drug-resistant seizures and a high mortality rate. In a double-blind, placebo-controlled trial, 120 children and young adults with Dravet syndrome were randomly assigned to receive either cannabidiol oral solution (20 mg per kilogram per day) or placebo, in addition to standard antiepileptic treatment (a median of 3.0 drugs). The authors reported that cannabidiol decreased the median frequency of convulsive seizures per month from 12.4 to 5.9, as compared with a decrease from 14.9 to 14.1 with placebo. A small percentage (5%) of patients in the CBD group became seizure free as compared to zero in the placebo group. Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhoea (31% vs 10%), loss of appetite (28% vs 5%) and somnolence (36% vs 10%). Other adverse effects noticed were vomiting, fatigue, pyrexia and abnormal