Safety, efficacy, and mechanisms of action of cannabinoids in neurological disorders

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Lancet Neurol 2019; 18: 504–12

Published Online March 22, 2019 http://dx.doi.org/10.1016/S1474-4422(19)30032-8

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In the past two decades, there has been an increasing interest in the therapeutic potential of cannabinoids for neurological disorders such as epilepsy, multiple sclerosis, pain, and neurodegenerative diseases. Cannabis-based treatments for pain and spasticity in patients with multiple sclerosis have been approved in some countries. Randomised controlled trials of plant-derived cannabidiol for treatment of Lennox-Gastaut syndrome and Dravet syndrome, two severe childhood-onset epilepsies, provide evidence of anti-seizure effects. However, small clinical trials of cannabinoids in other neurological disorders such as Huntington's disease, attention deficit hyperactivity disorder, and dementia, have not found any effect. Despite positive results in these two severe epilepsy syndromes, further studies are needed to determine if the anti-seizure effects of cannabidiol extend to other forms of epilepsy, to overcome pharmacokinetic challenges with oral cannabinoids, and to uncover the exact mechanisms by which cannabidiol or other exogenous and endogenous cannabinoids exert their therapeutic effects.

Introduction

Extracts of cannabis have been used to treat human diseases for thousands of years, but the isolation of biologically active cannabinoids and identification of their targets of action in humans, coupled with changing regional legislation regarding cannabis prohibition, have led to great interest in cannabinoid treatments among both patients and clinicians. Cannabinoid treatments are of particular interest for neurological disorders because of the identification of multiple potential targets of action in the CNS.[1] Most previous clinical research on the use of cannabinoids in neurological disorders has focused on spasticity and pain. As a result, nabiximols, a plant-derived mixture of cannabidiol and Δ^{9}tetrahydrocannabinol used as an oral mucosal spray, is approved in Brazil, Canada, Norway, Denmark, Iceland, Finland, the UK, Germany, Poland, Austria, Italy, Spain, Switzerland, Turkey, Israel, Australia, and New Zealand for the treatment of spasticity related to multiple sclerosis. Also, nabilone, a synthetic tetrahydrocannabinol approved in many regions of the world (including Europe, the USA, and Canada) for the treatment of nausea related to refractory chemotherapy, has been used as adjunctive treatment for refractory pain.[2]

Anecdotal data in humans, experimental animal models (eg, rodent models of acute seizures and chronic epilepsy) suggesting antiseizure and neuroprotective effects, and the absence of psychoactive effects of cannabidiol has led to an increasing interest in its potential therapeutic uses in patients with epilepsy.[3] Over the past 3 years, there have been several phase 2 and 3 randomised controlled trials of cannabidiol for treatment of different epilepsy syndromes that have reported efficacy, and several more randomised controlled trials are in progress. On the basis of these trials, the US Food and Drug Administration approved a purified, plant-derived cannabinoid, named cannabidiol, for the treatment of seizures in patients with Dravet syndrome and Lennox-Gastaut syndrome in 2018.[4]

At the same time that the clinical applications of cannabinoids have been explored, there have been efforts to better understand their CNS targets and how they interact with the endogenous cannabinoid signalling system in humans. In-vitro studies have identified CNS targets for many of the plant-derived cannabinoids beyond the canonical cannabinoid receptor subtypes CB_1 and CB_2 that can influence neurotransmitter release, neuronal excitability, inflammatory responses, gene transcription, and endogenous cannabinoid metabolism.[5] However, cannabinoids have been approved because of clinical studies, and the exact mechanisms by which they might relieve pain or control seizures are uncertain. Furthermore, little is understood about the long-term effects of therapeutic cannabinoid use. The availability of non-pharmaceutical cannabinoid preparations in some countries, and the general public's anecdotal belief in the efficacy of these so-called natural products, present unique challenges for clinical trials.[6]

In this Personal View, we critically discuss the latest understanding of the actions of cannabinoids in the CNS and what this knowledge might show about potential mechanisms of action. We also summarise clinical trials examining the safety and efficacy of cannabinoids in neurological disorders, and some of the challenges of interpreting the results of these studies. Although there is substantial use of non-standardised cannabis-based treatments in countries where such products are legal, we do not discuss clinical trials that use non-medicinal grade product, because controlled studies are scarce. The clinical trials of cannabis-based treatment of spasticity in patients with multiple sclerosis were done several years ago, and they will therefore only be described briefly for context, with the most focus on the new clinical trials of cannabidiol for patients with epilepsy.

Phytocannabinoids versus endocannabinoids

More than 110 potentially biologically active compounds such as cannabidiol and tetrahydrocannabinol have been isolated from the cannabis plant, and they are termed phytocannabinoids.[7] Most animal and clinical studies have focused on cannabidiol, either in combination with

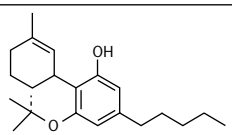
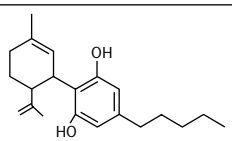
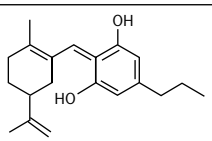
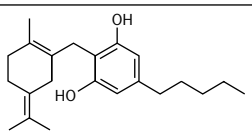
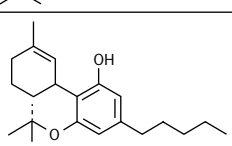
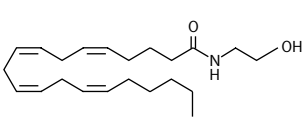
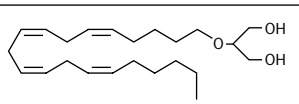
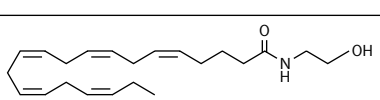
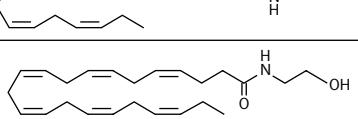
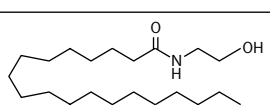
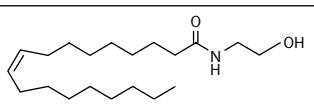
	Chemical structue	Cellular targets and effects with (A) activation, (I) inhibition, and (P) potentiation*	Proposed clinical indications[10–13]†
Phytocannabinoids			
Δ⁹-tetrahydrocannabinol		CB_1 (**A**), CB_2 (**A**), GPR55 (**A**), 5-HT_{3A} serotonin receptor (**I**), glycine receptors (**P**), PPARγ (**A**)	Antiemetic; treatment of post-traumatic stress disorder; treatment of sleep disorders; treatment of symptoms of dementia; appetite stimulant
Cannabidiol		CB_1 (**I**), CB_2 (**I**), GPR55 (**I**), 5-HT_{1A} (**P**) and 5-HT_{3A} (**I**) serotonin receptors, TRP channels (TRPV1 [**A**], TRPV4 [**A**], TRPM8 [**I**], TRPA1 [**A**]), cytochrome P450 (**I**), 15-lipoxygenase (I)	Antipsychotic; treatment of symptoms of Parkinson's disease; anxyolitic; treatment of post-traumatic stress disorder; anti-inflammatory or anti-nociceptive; treatment of seizures
Cannabidivarin		TRP channels (TRPV1 [**A**], TRPV4 [**A**], TRPM8 [**I**], TRPA1 [**A**])	Antiemetic; treatment of seizures
Cannabigerol		α2-Adrenoceptor (**A**), 5-HT_{1A} serotonin receptor (**I**), Lipoxygenases (**I**)	Appetite stimulant; treatment of Huntington's disease
Δ⁹-tetrahydrocannabivarin		CB_1 (**I**), CB_2 (**A**), 5-HT_{1A} serotonin receptor (**P**)	Anti-inflammatory or anti-nociceptive; treatment of seizures
ω-6 Endocannabinoids			
N-arachidonoylethanolamine (Anandamide)		CB_1 (**A**), CB_2 (**A**), GPR55 (**A**), GPR119 (**A**), TRPV1 (**A**), TRPM8 (**I**), PPARα (**A**), PPARγ (**A**), PPARδ (**A**), ligand-gated ion channels ($GABA_A$ [**P**], 5-HT3 serotonin receptor [**I**], nicotinic acetylcholine receptors [**I**], glycine receptors [**I**], glutamate NMDA receptors [**P**]), voltage-gated ion channels (T-type calcium Ca_v3 [**I**], 2TM [**I**] and 6TM [**A**] potassium channels)	..
2-arachidonoylglycerol		CB_1 (**A**), CB_2 (**A**), GPR55 (**A**), TRPV1 (**A**), PPARγ (**A**), PPARδ (**A**), ligand-gated ion channels ($GABA_A$ [P], nicotinic acetylcholine receptors [**I**], glycine receptors [**I**]), voltage-gated ion channels (2TM [**I**] and 6TM [**I**] potassium channels)	..
ω-3 Endocannabinoids			
N-eicosapentaenoylethanolamine		CB_1 (**A**), CB_2 (**A**), PPARγ (**A**)	..
N-docosahexaenoylethanolamine		CB_1 (**A**), CB_2 (**A**), PPARγ (**A**), 6TM potassium channels (**I**)	..
Endocannabinoid-like compounds			
N-palmitoylethanolamine		GPR55 (**A**), GPR119 (**A**), PPARα (**A**)	..
N-oleoylethanolamine		GPR55 (**A**), GPR119 (**A**), PPARα (**A**)	..

Figure 1: **Cellular targets, effects, and proposed clinical indications of the most studied phytocannabinoids and endocannabinoids**
5-HT=5-hydroxytryptamine (serotonin). GPR=G protein-coupled receptor. TM=transmembrane. TRP=transient receptor potential. TRPM8=TRP channel of melastatin type 8. TRPA1=TRP channel of ankyrin type 1. TRPV1/4=TRP channel of vanilloid 1/4. *For phytocannabinoids only targets activated at concentrations of 1 μM or less are listed. Also, note that all targets could be of therapeutic value, once the understanding of their role in phytocannabinoid activity or endocannabinoid signalling is improved. †Proposed clinical indications for phytocannabinoids are based on data from animal studies. ··=unknown.

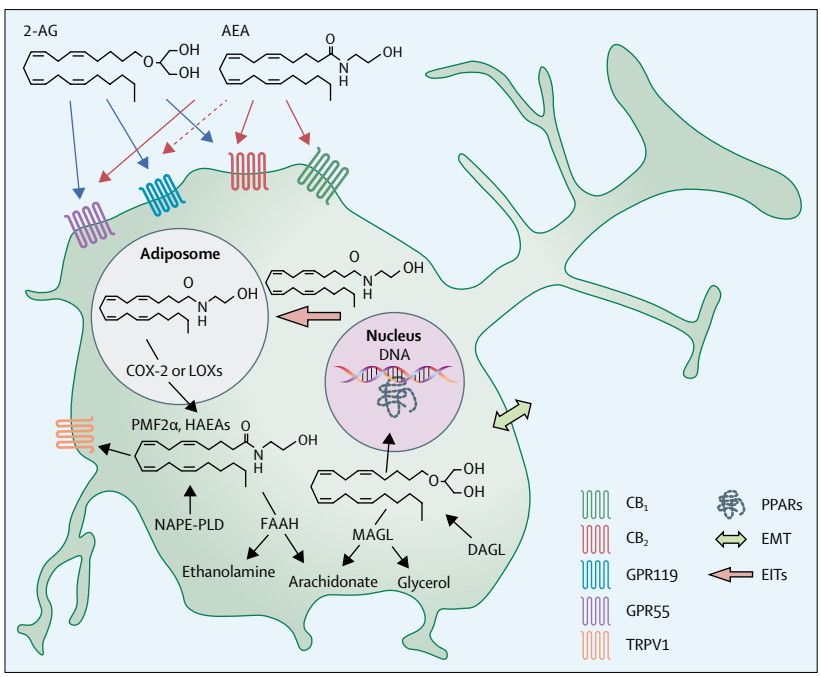


Figure 2: **The endocannabinoid system in the CNS**
Endocannabinoids like AEA and 2-AG can signal through various receptor targets on the plasma membrane (CB1, CB2, GPR55, GPR119, and TRPV1 binding of receptor targets are indicated by red arrows for targets of AEA and blue arrows for targets of 2-AG; dashed arrow indicates possible target) and in the nucleus (PPARs). Their biological activity is controlled by metabolic enzymes (NAPE-PLD and DAGL for the synthesis, FAAH and MAGL for the degradation), by transport mechanisms (acting both across the membrane via a putative EMT and intracellularly via EITs), and by accumulation and storage in intracellular organelles called adiposomes. In an adiposome, endocannabinoids can also be oxygenated by COX-2 and LOX isozymes into various oxygenated products (eg, PMF2α and HAEA, which are released from adiposomes and are involved in inflammatory processes). CB1 is the most abundant G-protein coupled receptor in the brain, whereas CB2 is expressed in neuronal cells only upon injury. NAPE-PLD and FAAH are the main metabolic enzymes for AEA, whereas DAGL and MAGL metabolise 2-AG. NAPE-PLD and DAGL cleave membrane phospholipids to release intracellular AEA, and DAGL cleave membrane phospholipids to release intracellular 2-AG, suggesting that endocannabinoids can be produced on demand from ready to use precursors when the cell receives appropriate stimuli. More information about endocannabinoid signalling in the cell can be found in Maccarrone and colleagues.[14,15] AEA=anandamide (N-arachidonoylethanolamine). 2-AG=2-arachidonoylglycerol. CB1=G-protein coupled type-1 cannabinoid receptor. CB2=G-protein coupled type-2 cannabinoid receptor. COX-2=cyclooxygenase-2. DAGL=diacylglycerol lipase α/β. eCB=endocannabinoid. EITs=eCB intracellular transporters. EMT=putative eCB transmembrane transporter. FAAH=fatty acid amide hydrolase. GPR55/119=G protein-coupled receptor 55/119. HAEAs=hydroxyanandamides. LOX=lipoxygenase. MAGL=monoacylglycerol lipase. NAPE-PLD=N-acylphosphatidyl-ethanolamine-specific phospholipase D. PMF2α,=prostamide F2α. PPARs=peroxisome proliferator-activated nuclear receptors. TRPV1=transient receptor potential vanilloid 1 channels.

tetrahydrocannabinol or alone, because of its therapeutic potential in various neurological disorders and absence of psychotropic effects.[8–10] While tetrahydrocannabinol binds and activates G protein-coupled type 1 (CB_1) and type 2 (CB_2) cannabinoid receptors, these receptors are blocked by cannabidiol through allosteric or indirect mechanisms that can be tissue-specific and cell-specific.[11] Tetrahydrocannabinol, cannabidiol, and other phytocannabinoids interact with other cellular targets[11–13] and might have clinical relevance (figure 1),[5,11–13] yet the biological background and underlying cellular and molecular mechanisms of these interactions are unclear.

The endogenous counterparts of phytocannabinoids, known as endocannabinoids, are agonists of CB_1 and CB_2, and include ethanolamides of ω-6 fatty acids or of ω-3 fatty acids (figure 1). Of note, despite overt differences in their chemical structures, phytocannabinoids share three-dimensional aspects of their structure with endocannabinoids.[9,10] This resemblance is the reason why phytocannabinoids can bind the same targets that recognise endocannabinoids in the cell.[11–13] In addition to phytocannabinoids and endocannabinoids, there are endocannabinoid-like compounds (figure 1), but these do not activate CB_1 and CB_2. Both endocannabinoids and endocannabinoid-like molecules have manifold biological activities at the periphery (eg, on the cardiovascular system, gastrointestinal tract and liver, immune system, muscles and bones, reproductive cells, and skin)[14] and within the CNS (eg, on dopaminergic, GABAergic and glutamatergic transmission, on induction of long-term depression and inhibition of long-term potentiation, on control of pain initiation, wake and sleep cycles, thermogenesis and appetite, and on impairment of working memory and of memory consolidation).[5,15,16] Phytocannabinoids have terpenophenolic structures (figure 1) that, unlike the fatty acids of endocannabinoids, cannot be synthesised nor hydrolysed by the body. This attribute seems to be important, because the biological activity of endocannabinoids is tightly regulated through metabolic control.[5,14–16]

The endocannabinoid system

The manifold actions of endocannabinoids are subjected to a stringent control that depends on biosynthetic enzymes and even more on hydrolytic enzymes (figure 2). Such a stringent control is further refined by distinct transporters, which facilitate the movement of endocannabinoids both across the plasma membrane and intracellularly, and by storage of endocannabinoids in organelles like adiposomes. Altogether, receptors, enzymes, and transporters form the endocannabinoid system, which drives timely delivery of the correct endocannabinoid (in the right concentration) to its target (figure 1, 2). It is the biochemical arsenal of the endocannabinoid system that allows endocannabinoids to act as highly sophisticated signals, which are capable not only of mutual interactions and cross-checks,[5,14–16] but also of acting at large as a synaptic circuit breaker that sets the threshold for neuronal excitability, with a huge effect on several physiological conditions and neurological disorders including epilepsy.[8]

On the basis of the complexity of the endocannabinoid system, it should be appreciated that any perturbation of signalling by compounds such as phytocannabinoids—which are able to trigger the same receptors as endocannabinoids but escape metabolic control—can lead to unpredictable and potentially detrimental side-effects. It is also possible that individual differences in either the positive or negative effects of phytocannabinoids, or any drugs that target endocannabinoids, might depend on individual differences in components of the endocannabinoid system, and hence in signalling.

Although our understanding of the endocannabinoid signalling system and its regulation has greatly expanded, the clinical studies on treatment of neurological disorders have focused on the two most abundant phytocannabinoids—cannabidiol and tetrahydrocannabinol—because of a history of animal studies and anecdotal human experience that preceded our understanding of the endocannabinoid system.[17] The mechanism by which these phytocannabinoids and their analogues directly or indirectly modulate the endocannabinoid system is only started to be studied now.

Clinical trials of cannabidiol and other cannabinoids for epilepsy

The first large epilepsy trial of cannabidiol was an open-label trial of a purified oral cannabidiol solution starting with 2–5 mg/kg per day, and titrated to a maximum daily dose of 25 mg/kg or 50 mg/kg per day (dependent on study site) in 214 patients (aged 1–30 years) with severe, intractable epilepsy.[18] The study primarily assessed safety and pharmacokinetics; 167 (78%) patients were included in the safety analysis and 137 (64%) in an efficacy analysis, which focused on motor seizures. The mean cannabidiol dose achieved was approximately 23 mg/kg per day. The median change in motor seizures was −34·6% (IQR −66·7 to 0). This study established that cannabidiol had an acceptable safety profile, leading to subsequent randomised, placebo-controlled trials of adjunctive cannabidiol among patients with Dravet syndrome and patients with Lennox-Gastaut syndrome.

A subsequent trial enrolled 120 children with Dravet syndrome, aged 2–18 years who experienced four or more convulsive seizures per month despite receiving one or more antiepileptic drugs.[19] Patients received 20 mg/kg per day of cannabidiol or placebo during a 2-week titration period and 12-week maintenance period. 108 (90%) patients completed the study. Patients treated with cannabidiol had a significantly greater reduction in convulsive seizures per month after drug initiation (from median of 12·4 seizures per month at baseline to 5·9 seizures over the treatment period) compared with those on placebo (14·9 seizures per month at baseline to 14·1 seizures).

There have been two trials enrolling patients with Lennox-Gastaut syndrome, although one trial[20] of 225 patients had a three-arm design (patients received either 10 mg/kg per day of cannabidiol, 20 mg/kg per day of cannabidiol, or placebo), whereas the other trial[21] of 171 patients had only two groups (patients received either 20 mg/kg per day of cannabidiol or placebo). Enrolled patients (aged 2–55 years) in each trial had at least two drop seizures, defined as any seizure (tonic, atonic, or tonic-clonic) that could lead to the patients falling, per week, and the trial duration in each trial was 28 days, followed by 2 weeks of titration and 12 weeks of maintenance dosing. In both studies, patients randomised to cannabidiol had a significant reduction in drop seizures. In the three-arm study,[20] the median percent reduction of drop seizures per month from baseline was 41·9% for the 20 mg/kg per day cannabidiol group, 37·2% for the 10 mg/kg per day cannabidiol group, and 17·2% for the placebo group. In the two-arm study,[21] median percent reduction in drop seizures per month from baseline was 43·9% for the 20 mg/kg per day cannabidiol group and 21·8% for the placebo group. Some patients who received cannabidiol (eight in the three-group trial, three in the two-group trial) were free of drop seizures during the entire maintenance period.

Although the largest trials of cannabidiol have been in patients with Dravet syndrome or Lennox-Gastaut syndrome, there have been some small, open-label studies of other types of epilepsy that have reported improvement in seizure frequency with cannabidiol, including a study of seven children with febrile infection-related epilepsy syndrome,[22] and case-series including other intractable epilepsy syndromes (Doose syndrome, eight patients; Aicardi syndrome, 19 patients) and aetiologies (duplication 15q syndrome, eight patients; cyclin-dependent kinase-like 5 related epilepsy, 20 patients).[23] A cannabidiol solution is also currently undergoing testing in a randomised, placebo-controlled trial for seizures associated with tuberous sclerosis complex (NCT02544763). Additionally, clinical trials in adults with drug-resistant focal epilepsy are in progress for a transdermal formulation of a synthetic cannabidiol (ACTRN12616000510448) and cannabidavarin, another non-psychoactive phytocannabinoid (NCT02369471). Cannabidiol is also being examined for treatment of infantile spasms (NCT03421496).

Challenges in assessing efficacy

Although the three randomised, placebo-controlled trials of cannabidiol[19–21] in patients with either Dravet syndrome or Lennox-Gastaut syndrome are promising, there are several caveats related to efficacy that must be addressed in future studies. One potential confounder is that cannabidiol is a potent inhibitor of the hepatic P450 enzymes CYP2C19, CYP2D6, and CYP2C9 at micromolar concentrations. This attribute can lead to important drug interactions as these pathways are also involved in the metabolism of antiepileptic drugs.[24,25] This aspect is particularly relevant for patients with drug-resistant epilepsy such as Dravet syndrome or Lennox-Gastaut syndrome, whose multidrug regimens often include clobazam. Several studies have shown that cannabidiol increases the serum concentrations of *N*-desmethyl-clobazam, an active metabolite of clobazam with a long serum half-life metabolised by CYP2C19, by 200–400%.[26–28] This interaction is likely to be clinically important since patients taking clobazam are more likely to experience sedation with cannabidiol than those not taking clobazam.[18,28] A substantial number of participants in each trial (78 [65%] of 120 in the Dravet syndrome trial, and 194 [49%] of 393 in the Lennox-Gastaut syndrome trial) were receiving clobazam. Although the effect of cannabidiol on clobazam concentrations in serum can

be measured by standard assays, *N*-desmethyl-clobazam serum concentrations are not typically measured. When clobazam concentrations rose in the trials, doses were often adjusted, but a study[26] in 13 patients with refractory epilepsy taking both cannabidiol and clobazam reported that *N*-desmethyl-clobazam concentrations became substantially elevated (at times, elevated to double the baseline concentration) after the addition of cannabidiol whereas clobazam concentration changed little from baseline. The contribution of higher *N*-desmethyl-clobazam exposure to the efficacy observed in the randomised controlled trials cannot be determined, because the trial participants were not stratified on the basis of the use of clobazam. In a randomised, dose-ranging safety trial of cannabidiol in 24 patients with Dravet syndrome,[28] patients treated with stiripentol, a commonly used antiepileptic drug for Dravet Syndrome and a potent CYP2C19 inhibitor, did not have changes in *N*-desmethyl-clobazam concentrations with the addition of cannabidiol. Assessing the effect of cannabidiol on seizures in patients taking both clobazam and stiripentol might help to disambiguate direct antiseizure actions of cannabidiol from those mediated by pharmacokinetic interactions. Finally, the studies reporting effects of cannabidiol on seizures are only 3 months in duration and the long-term efficacy of cannabidiol in these severe epilepsies is under study in long-term, open-label extension studies (NCT02224573).

Clinical trials of cannabidiol and other cannabinoids for multiple sclerosis

Several controlled trials to assess the safety and efficacy of nabiximols on symptoms of multiple sclerosis were done over a decade ago, and their results are summarised briefly. The first trial[29] compared the ability of nabiximols versus placebo to treat the five most troublesome symptoms (spasticity, spasms, bladder problems, tremor, and pain) of the 160 randomised patients with multiple sclerosis. Although there was no overall difference in a composite symptom score, there was significant improvement among the 37 participants who reported spasticity as their most troubling symptom and received nabiximols, compared with those who received placebo. This improvement was sustained in the long-term extension study over a mean 1·19 years of follow-up.[30] A second trial of 337 patients with moderate-to-severe spasticity, reported symptom reduction (as measured by a patient-reported numerical rating scale) with nabiximols compared with placebo.[31] However, the intention-to-treat analysis did not show a significant difference, probably because of the high percentage of dropout (about 10%) in both groups.[31] As a result of these studies, the American Academy of Neurology evidence-based review concluded that nabiximols was probably effective in reducing patient-reported symptoms of spasticity at 6 weeks (one Class 1 study), but probably ineffective in reducing objective measures of spasticity at 6 weeks (one Class 1 study).[32] Subsequently, two additional enrichment trials were done.[33,34] In these trials, participants entered a single-blind 4-week period (phase A) to identify responders to nabiximols treatment, who were then randomly assigned to receive either nabiximols or placebo in phase B. In one study,[33] 241 (42%) of 572 participants continued into phase B, and in the other,[34] 106 (55%) of 191 participants continued into phase B. In both studies, patients assigned to nabiximols were significantly more likely to have a 30% or greater reduction in spasticity than those assigned to placebo.

Nabiximols was also studied in participants with pain associated with multiple sclerosis, in a placebo-controlled trial[35] in which a numeric rating scale was used as the outcome measure. This study included an initial parallel group, randomised, placebo-controlled phase with 339 participants (phase A) and a subsequent, smaller randomised withdrawal phase with 58 participants (phase B). Analysis of phase A did not find response to treatment, defined as an improvement of 30% or more in patient's mean pain score from baseline to the last week of treatment, but there was a significant difference in time to treatment failure during phase B.

The mixed results of the studies on spasticity and pain, coupled with some success when enrichment trials were done, might suggest that only a subset of patients will benefit from treatment with cannabinoids. However, enrichment trials might be confounded by the fact that all participants are exposed to the treatment before randomisation, which can lead to unblinding. The characteristics of likely responders are unknown. On the basis of this scarce and conflicting evidence, for the majority of patients with multiple sclerosis, it seems reasonable to try conventional anti-spasticity therapies first, and reserve nabiximols for those who do not respond or tolerate these treatments.

Clinical trials of cannabidiol and other cannabinoids for other neurological disorders

Cannabinoids, mostly as tetrahydrocannabinol and cannabidiol mixtures from plant extracts or synthetic tetrahydrocannabinol, have been studied for analgesia in neuropathic pain. A Cochrane systematic review,[36] which included 16 studies with 1750 patients treated for 2–26 weeks with cannabinoids, concluded that there was low-quality evidence for a modest improvement in patients having over 50% reduction in pain ratings compared with placebo (21% *vs* 17%), but with more adverse events leading to withdrawal (10% *vs* 5%). The quality of evidence was considered to be low because of several factors, including evidence for publication bias and small study size.[36] A systematic review of cannabinoids, which included 22 studies with 795 children, for the treatment of pain also concluded that the evidence base was weak and did not support treatment recommendations.[37]

Studies in other neurological conditions have been scarce. A pilot trial of nabiximols in 26 patients with Huntington's disease did not show a benefit in motor, cognitive, behavioural, or functional outcomes compared

with placebo.[38] There was no effect of nabiximols compared with placebo on cognitive performance and activity level (head movements) in another pilot trial of 30 adults with attention deficit hyperactivity disorder.[39] Two small randomised crossover studies of behavioural disturbances (22 participants)[40] and gait (18 participants)[41] in patients with dementia found that, although well tolerated, there were no effects of oral tetrahydrocannabinol on assessed symptoms (eg, agitation, night-time behavioural disturbances, anxiety and other mood symptoms, mobility, and falls).

Clinical pharmacology

The clinical pharmacology of cannabidiol and tetrahydrocannabinol has been reviewed elsewhere.[25] Briefly, both cannabidiol and tetrahydrocannabinol are lipophilic molecules with poor water solubility. For this reason, previous clinical trials of purified cannabidiol have used an oral solution dissolved in sesame oil, and nabiximols is an oral mucosal spray that uses ethanol as the primary excipient. Because of its high lipophilicity and substantial first pass hepatic metabolism, bioavailability of oral cannabidiol is poor (6–19%) and variable.[25] For instance, in a dose-ranging study, 34 patients with Dravet syndrome were randomly assigned to add-on either 5 mg/kg, 10 mg/kg, or 20 mg/kg of cannabidiol oral solution or placebo to their antiepileptic drug regime; the coefficient of variability for plasma cannabidiol concentrations obtained 2·5 h after drug administration in patients taking the drug chronically was greater than 65%.[28] There is a substantial increase in oral bioavailability of cannabidiol and tetrahydrocannabinol when they are taken with food.[42] The effect of this variability on clinical efficacy for seizures or other conditions is unknown, but transdermal delivery mechanisms for cannabidiol have been developed to improve bioavailability and reduce variability in plasma concentrations,[43] and are currently in clinical trials for patients with epilepsy (ACTRN12616000510448) and patients with Fragile X syndrome (NCT03614663).

Safety and tolerability

Much of the knowledge regarding safety and tolerability of cannabinoids, including synthetic tetrahydrocannabinol analogues, used in neurological disorders came from studies in adults with multiple sclerosis for spasticity, pain, and tremor. In these studies of cannabinoids—mostly a mixture of tetrahydrocannabinol and cannabidiol in the form of cannabis extracts or nabiximols—common adverse effects included nausea, weakness, behavioural and mood changes, fatigue, dizziness, and intoxication. In a pooled analysis of short-term (ie, up to 6 months) studies, 112 (7%) of 1619 patients with multiple sclerosis, neuropathic pain, and movement disorders stopped treatment because of adverse effects compared with 25 (2%) of 1118 patients in the placebo group.[32] In a small study of 20 patients with multiple sclerosis who used cannabis chronically for symptom relief and 19 patients matched by age, sex, and disability who did not use cannabis, chronic cannabis use was associated with reduced cognitive function and diminished volumes of subcortical, medial temporal, and prefrontal regions on structural MRI.[44] Tetrahydrocannabinol exposure was not examined in this study and the contribution of specific phytocannabinoids to these reported chronic effects is unknown. Two small randomised controlled trials (including) of purified cannabidiol in 88 adults[45] and 36 adults[46] with schizophrenia did not show exacerbation of psychiatric symptoms (eg, agitation or psychosis) suggesting that cannabidiol has no psychoactive effects even in adults who might be most predisposed to negative psychotropic effects of medications.

Randomised controlled trials[19–21] and prospective open-label studies[23,47,48] have assessed the short-term safety and tolerability of cannabidiol in children and young adults with severe epilepsies. In randomised controlled studies,[19–21] adverse events occurred frequently in treatment groups but were also common among placebo groups, probably related to the high overall medication burden and disease severity in these patients. The most common adverse events in all studies were drowsiness and diarrhoea and other gastrointestinal side-effects (possibly related to sesame oil used as the solvent in cannabidiol solutions). Serious adverse events attributed to cannabidiol included seizure exacerbations or status epilepticus, transaminitis, thrombocytopenia, and severe diarrhoea or appetite loss. In the Dravet syndrome trial,[19] 57 (93%) of 61 cannabidiol-treated patients and 44 (75%) of 59 placebo-treated patients reported adverse effects. Although most reported adverse effects were mild to moderate, adverse effects led to withdrawal in eight (13%) of 61 cannabidiol-treated patients and one (2%) of 59 placebo-treated patients.[19] In the Lennox-Gastaut syndrome trials, 6–12 (8–14%) of 76–86 patients in high-dose groups (20mg/kg per day), one (1%) of 73 patients in the single low-dose group (10 mg/kg per day), and zero to one (≤1%) of 76–85 patients in the placebo groups withdrew because of adverse effects.[20,21] A meta-analysis of the three randomised controlled trials[19–21] and two small older trials performed in the 1980s for epilepsy suggested that the relative risk for adverse events for participants treated with cannabidiol was 1·23 (95% CI 1·10–1·38) compared with placebo; the relative risk for serious adverse events was estimated to be 2·40 (1·17–4·93).[49]

Elevated transaminase concentrations, defined as elevation of three times or more the upper limit of normal, occurred in 28 (13%) of 296 cannabidiol-treated patients compared with two (1%) of 220 placebo-treated patients in the three recent randomised controlled trials.[18,19,21] In a majority of cases, the increases in transaminase concentrations were self-limited and did not lead to drug discontinuation. Most patients who had elevated liver function values were also taking concomitant valproic acid, suggesting that cannabidiol might potentiate liver injury related to valproic acid. Scarce long-term safety data are available for

Search strategy and selection criteria

Databases including PubMed and Google Scholar were searched for papers published between Jan 1, 2015, and Nov 16, 2018, using the terms "Cannibinoids OR Cannabidiol OR Tetrahydrocannabinol OR CBD OR THC AND clinical trial". Search results were reviewed and primary studies and systematic reviews and meta-analyses related to neurological disorders were identified for inclusion in this Personal View. Additionally, we did a search in ClinicalTrials.gov with the term "Cannabidiol OR Cannabinoids AND clinical trial" to identify ongoing clinical trials registered as of Nov 16, 2018. Additional query terms included "Cannabinoid OR Cannabidiol AND Pharmacokinetics AND human" between Jan 1, 2013, and Nov 16, 2018, to identify relevant new studies and systematic reviews in PubMed and Google Scholar.

cannabidiol in either paediatric or adult patients with severe epilepsies. Results from a single prospective open-label study of 607 patients with treatment-resistant epilepsies given purified cannabidiol for up to 96 weeks supported previous observational and clinical trial data showing that add-on cannabidiol was generally well tolerated by these patients.[48]

Conclusions and future directions

There is emerging clinical evidence that some phytocannabinoids might be relatively safe and effective treatments for neurological disorders such as severe epilepsy syndromes,[19–21] and for pain and spasticity in patients with multiple sclerosis.[29–35] Studies of cannabinoids for the treatment of multiple sclerosis[29–31,33–35] have several methodological concerns, but as a whole, suggest a modest effect in most cases, possibly with some patients classified as high responders. The effects of cannabidiol for seizures in patients with Dravet syndrome[19] and patients with Lennox-Gastaut syndrome[20,21] might be more reliable, but the confounding by cannabidiol's interaction with clobazam[26] makes the true independent effect difficult to determine as patients in the studies were not stratified by presence of clobazam as a background drug. It is also unknown if cannabidiol reduces seizures in more common forms of epilepsy, such as focal epilepsy and idiopathic generalised epilepsy, a question of great interest to patients and their clinicians. Although a phase 2 study (ACTRN12616000510448) has been completed in adults with focal seizures, this study is not yet published and further trials are likely to be necessary. Trials in other epilepsies such as in patients with infantile spasms (NCT03421496) and patients with tuberous sclerosis (NCT02544763) are in progress. Given the scarce safety and efficacy data, it might be premature to recommend cannabidiol to patients with more common forms of drug-resistant epilepsy if other tolerated and effective treatments have not yet been tried. It is important to understand that cannabinoids are not without risk, and prescribing clinicians should be aware of potential side-effects and drug interactions. Additionally, more studies are also needed to determine long-term safety, especially the effect on brain development and teratogenicity. Despite the public perception of cannabis-derived drugs as a so-called natural treatment, it is unknown if phytocannabinoids are safer and better tolerated than other approved therapies as there are no comparative studies. Finally, it is not appropriate to extrapolate the results of trials of standardised preparations to other non-standardised, non-regulated medical cannabis products.[50]

Evidence from large, well controlled studies for the efficacy of phytocannabinoids for other neurological disorders is scarce and the available data are often limited to anecdotal reports and animal experiments. Additional clinical trials in progress (eg, NCT03614663 and NCT03087201) might provide evidence of efficacy of cannabinoids for other neurological disorders, but early pilot or early clinical studies[36,40,41] in patients with dementia and pain have not shown substantial efficacy in symptom reduction. One possible reason for conflicting results from clinical trials of phytocannabinoids is that it is not yet exactly clear how these molecules exert their therapeutic effects. The endocannabinoid system is a complex ensemble of lipid signals and their receptors, enzymes, and transporters; how phytocannabinoids affect this endogenous prohomoeostatic system is not well understood. It is not even clear if cannabidiol exerts its anti-seizure effect through the endocannabinoid system at all, instead potentially acting on non-selective cation channels, presynaptic G-protein receptors, or other targets that influence neuronal excitability or synaptic transmission.[51] Better understanding of the key molecular targets of phytocannabinoids in neurological disorders could lead the way towards additional novel therapies. However, elucidating lipid-based signalling systems is difficult. For instance, it took almost 30 years since the discovery of the CB_1 receptor, which is fully embedded in the plasma membrane and hence is hard to isolate and investigate, to obtain its three-dimensional structure.[52] Scarcity of knowledge about molecular structure of most elements of the endocannabinoid system prevents the development of selective tools to address their effect on signalling pathways.

Contributors

DF, JAF, and MM drafted and critically reviewed the manuscript. All authors contributed equally to this manuscript.

Declaration of interests

DF receives salary support for consulting and clinical trial related activities performed on behalf of The Epilepsy Study Consortium, a non-profit organisation, and receives no personal income for these activities. New York University receives a fixed amount from the Epilepsy Study Consortium towards DF's salary. Within the past 3 years, The Epilepsy Study Consortium received payments for research services performed by DF from Acorda, Adamas, Alexza, Axcella, Biogen, Biopharm, CuroNZ, Eisai, Empatica, Engage, GW Pharma, Pfizer, Pfizer-Neusentis, Marinus, SK Life Sciences, Takeda, Upsher Smith, Zogenix, and Zynerba. DF has also served as a paid consultant for Eisai, Liva Nova, Penumbra, Supernus, and UCB Inc; received honorarium from Neuropace Inc;

receives research support from Adamas, UCB Inc, Neuropace Inc, Epitel, and Empatica; and holds equity in Neuroview Technology. JAF receives New York University salary support from the Epilepsy Foundation, and for consulting work and attending Scientific Advisory Boards on behalf of the Epilepsy Study Consortium in the past 3 years for Acadia, Acorda, Adamas, Addex, Aeonian, Alexza, Anavex, Axcella Health, Axovant, Biogen, BioPharm Solutions, Biomotiv, Blackfynn, Bloom Science, Bridge Valley Ventures, Cavion, Cerebral Therapeutics, Cerecor, Cerevel, Clinilabs, Concert Pharmaceuticals, Covance, CuroNZ, Eisai, Empatica, Engage Therapeutics, Epitel, Georgia Regents University, GlaxoSmithKline, GW Pharma, Idorsia, Impax, Ionis, Johnson and Johnson Pharmaceuticals, Marinus, MonosolRx, Monteris, Nestle Health-Science, Neurelis, Novartis, Otsuka Pharmaceutical Development, Ovid Therapeutics Inc, Pfizer, Pfizer-Neusentis, Redpin, Roivant, Sage, Sancillio, SciFluor, Shire, SK Life Sciences, Springworks, Stoke, Sunovion, Supernus, Takeda, UCB Inc, Ultragenyx, Upsher Smith, Vyera, West Therapeutic Development, Xenon, Xeris, Zogenix, and Zynerba. JAF has also received research grants from Acorda, Adamas, Alexza, Biogen, BioPharm Solutions, Cavion, Eisai Medical Research, Engage, LCGH, Lundbeck, Neurelis, Ovid, Pfizer, SK Life Sciences, Sunovion, UCB, and Zogenix and grants from the Epilepsy Research Foundation, Epilepsy Therapy Project, Epilepsy Study Consortium, Milken Family Foundation, and National Institute of Neurological Disorders and Stroke. JAF is on the editorial board of the *Lancet Neurology* and *Neurology Today*. JAF is scientific officer for the Epilepsy Foundation for which New York University receives salary support. JAF was formerly the chief scientific officer of the Epilepsy Therapy Project and received salary support for that role. JAF has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Epilepsy Therapy Project, Acorda, Adamas, Axovant, Biogen, Blackfynn, CuroNz, Eisai, Engage, GlaxoSmithKline, GW Pharma, Idorsia, Nestle Health-Science, Neurelis, Novartis, Otsuka, Ovid, Pfizer, Redpin, Sage, Sunovion, Takeda, UCB, Ultragenyx, Zogenix, and Zynerba. MM is on the Scientific Advisory Board of Phytecs Inc and of InMed Pharmaceuticals Inc. In the past 5 years, he has received consultation fees from Almirall, and research grants from Hoffmann-La Roche and GW Pharmaceuticals. None of these professional engagements affected his contribution to the present article.

Acknowledgments

The authors thank Monica Bari (Tor Vergata University of Rome, Italy) for her kind help with the artwork.

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