

A perspective on cannabinoids for treating epilepsy: do they really change the landscape?

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Conflict of interest statement

Professor Cross has been a principal investigator for studies with GW Pharma, Zogenix, Vitaflo, Marinius and Ovid Pharmaceuticals, remuneration for which has all been made to her department. Her department has received honoraria for speaker and advisory board engagements for GW Pharma, Zogenix, Takeda and Nutricia. She is a recipient of grants from National Institute Health & Research, SPARKS, Great Ormond Street Hospital Charity and EPSRC.

Prof Cock's deceased son was on Cannabidiol for around 18m as part of a UK trial, prior to his death (unrelated) in 2016. Prof Cock has been a principal investigator for studies with GWPharma, Novartis and Bial, with remuneration to her department. She has received honoraria for speaker and advisory board engagements for Sage Pharmaceuticals Ltd, Eisai Europe Ltd, UCB Pharma Ltd, European Medicines Agency, UK Epilepsy Nurse Specialist Association, non-financial support from Special Products Ltd, grants from U.S NIH Institute of Neurological Disorders and Stroke, nonfinancial support from International League Against Epilepsy, Status Epilepticus Classification Task Force and Epilepsy Certification (education) Task Force, and non-financial support from European Academy of Neurology.

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1. Introduction

In June 2018, US authorities recommended approval of the first cannabis based treatment to treat drug resistant seizures in Dravet and Lennox Gastaut Syndromes, based on data from randomised controlled trials supported by selected case videos, and “emotional testimony” from parents (Dyer, 2018). The same month the UK government requested a review into “medicinal cannabis” by the Chief Medical Officer, with around 350,000 people in the UK already known to be using artisanal (non-pharmaceutical grade, available over the counter or online without prescription) preparations, representing a 4 fold increase since October 2016 (Grierson and Busby, 2018). Within a month an intention to reclassify “medicinal cannabis” was put forward and an aim to ensure availability on prescription in the UK by Autumn 2019. An initial step involved specialists being able to apply to an expert advisory panel for cases of “exceptional and unmet clinical need” (Torjesen, 2018); subsequently legislation changed on 1st November 2018 moving cannabis based medicinal products (CBMPs) containing tetrahydrocannabinol from schedule 1 to schedule 2, so in theory enabling prescription of such products where clinically justified in accordance with published interim guidelines. This article reviews the truth behind the hype, to support clinicians in discussions with patients.

2. Historical context

Cannabis is the third most consumed recreational drug worldwide, used by an estimated 4% of the population, totalling over 192 million uses in 2016 (Budney et al., 2019). That cannabis may have medicinal potential has also been recognized for thousands of years (Santos et al., 2015). Scientific interest dates from the 1960s, since when the many active components of the cannabis plant have been identified, and the endogenous (endocannabinoid) system characterized (O’Connell et al., 2017; Santos et al., 2015). Cannabis has several strains, and contains hundreds of chemicals that occur naturally in the plant. The two most important are cannabidiol (CBD) and tetrahydrocannabinol (THC). The term “medicinal cannabis” covers a range of products, some containing CBD only, others with both CBD and THC in varying proportions, in addition to a large number of other cannabinoids and compounds.

Over the last few years a largely public led movement, driven by unmet need, anecdotal reports in social media and mainstream news, have achieved approval for medicinal cannabis preparations in the almost all US States, and at least 40 other countries (Thomas and Cunningham, 2018). Laws vary from strict decriminalisation, through carefully regulated medical use, to full legalization including for personal recreational purposes in Canada, Uruguay and 8 US States (Barnes, 2018; Hall, 2018). This presents both opportunities and new challenges for policymakers, clinicians and researchers.

3. Mechanism of action and pre-clinical studies

Endocannabinoids are small lipid messengers synthesized ‘on demand’ in an activity-dependent manner through cleavage of membrane phospholipids, and intimately involved in the regulation of cortical excitability (Katona and Freund, 2008). The endocannabinoid system thus is an attractive target for drug development in epilepsy. To date, two cannabinoid receptors (CB1 and CB2) have been

identified. CB1 receptors are widely expressed in the CNS, mainly localized on presynaptic terminals. CB2 receptors are mainly located outside the CNS but are expressed by microglia during inflammatory processes as well as in brainstem neurons (De Caro et al., 2017). Of the hundreds of plant derived cannabinoids, THC, delta-9-tetrahydrocannabinol (THCV), cannabidiol (CBDV), delta-8-tetrahydrocannabinol (delta-8-THC), cannabidiol (CBD) and especially CBD have anticonvulsant effects. THC exerts its antiseizure effect mainly as a partial agonist for CB1 receptors, but also has demonstrable pro-convulsant effects in some models and is associated with the development of tolerance and adverse consequences on behaviour and cognition in vivo (Santos et al., 2015). Most interest thus far has focussed on CBD, though the key mechanism(s) of action remain elusive. At physiologically achievable (nmolar) concentrations CBD has low affinity for CB1 or CB2 receptors, but may have an indirect modulatory effect by blocking the breakdown of the endocannabinoid anandamide (Brodie et al., 2015). Other demonstrable effects that may reduce neuronal hyperexcitability, and potentially inflammation, including effects on GPR55 g-protein-coupled receptor 55 (GPR55), transient receptor potential vanilloid 1 (TRPV1) channels and equilibrative nucleoside transporter 1 (ENT1) adenosine reuptake pumps are summarized in Figure 1. Preclinical studies further suggest that GPR55 might be a primary target of action in a well validated mouse model of Dravet syndrome (Kaplan et al., 2017). Others have also postulated there may be targeting of abnormal sodium channels, modulation of voltage-dependent anion selective channel protein (VDAC1), and of Tumour necrosis factor alpha release (Bialer et al., 2018; Brodie et al., 2015). Presynaptic CBD also has affinity for 5-Hydroxytryptamine (5HT) 1a and 2a receptors, but pre-treatment with serotonin antagonists doesn't block the antiseizure effects, so this may not be relevant (Brodie et al., 2015).

CBD is also postulated to have neuroprotective effects. High doses of CBD, 100mg/kg given either at termination of kainite induced status epilepticus in rats, or 90 minutes later was associated with a significant reduction in atrophy and death of parvalbumin (PV)-expressing and cholecystokinin (CCK)-expressing interneurons 2 weeks later (Khan et al., 2018). Parallel in vitro brain slice studies, using bath application of 10µM CBD in in vivo (kainic acid) and in vitro (Mg²⁺+free solution) seizure models demonstrated dampened excitability at unitary synapses between pyramidal cells, but enhanced inhibitory synaptic potentials elicited by fast spiking and adapting interneurons at postsynaptic pyramidal cells. CBD also restored impaired membrane excitability of PV, CCK and pyramidal cells in a cell-type specific manner.

Pre-clinical studies indicate CBD is a relatively potent anticonvulsant in wide range of acute provocation and spontaneous seizures models (Santos et al., 2015). The most recently published data have arisen from a collaboration between the US National Institute for Health, GWPharma who manufacture the first CBD formulation to be licensed for epilepsy (Epidiolex™) and the University of Reading, UK (Patra et al., 2019). Using a standard battery of acute provoked seizure models in mice (maximal electric shock, pentylenetetrazol, 6Hz stimulation), and corneal kindled seizures, pre-treatment with CBD prevented seizures at doses well below those which impaired motor function. Of note, they also demonstrated a far greater margin between effective doses and motor adverse effects compared to those reported for valproate and phenobarbitone. An intravenous dose of 10mg/kg 1 hour prior to pilocarpine induced status epilepticus similarly attenuated seizures, as has also been shown in previous studies using the more traditional intraperitoneal route. The effect was less marked than with phenobarbitone (30mg/kg), though this might reflect dose differences. CBD efficacy after the onset of status epilepticus, or (as would be clinically relevant) in benzodiazepine refractory status epilepticus has yet to be evaluated. In rats developing chronic post-status epilepticus temporal lobe epilepsy, administration of CBD in drinking water after the onset of spontaneous seizures for up to 8 weeks was associated with significantly fewer seizures (video monitoring) by the end of treatment than in those receiving placebo, or a comparative time period at the start of treatment. Memory errors were also partially ameliorated in CBD treated animals,

although the extent to which this reflected reduced seizure burden versus a direct neuroprotective effect is speculative. The possibility of some disease modifying effect, against both epileptogenesis and associated consequences is undoubtedly attractive, though as yet unproven.

The oral bioavailability of CBD is less than 10%, with low water solubility and significant first pass metabolism, but then rapid distribution into fat including brain. It is highly protein bound, reaching peak serum levels within 90-120minutes, and with a $\frac{1}{2}$ life of 18-32 hours (Bialer et al., 2018). The fat content of a meal can lead to significant increases in bioavailability (Birnbaum et al., 2019), contributing to considerable variability in drug exposure with oral products. A increasing range of alternative formulations (intranasal, transdermal, transmucosal) are now being studied in the hope of addressing these limitations (Bruni et al., 2018). Of note, most of the mechanisms of action demonstrated in vitro require micromolar concentrations. Serum levels of oral CBD and it's metabolites increase proportionally with dose (Devinsky et al., 2018b), achieving serum concentrations in the pico to nanomolar range. What concentrations are achieved in the brain with standard dosing is unknown, and may well be higher given the fat solubility. An interaction with *N*-desmethylclobazam has been demonstrated, likely due to CBD inhibition of cytochrome p450 subtype 2C19, with other potential interactions still under study. This may be particularly relevant to the efficacy in Dravet syndrome, where patients are typically on clobazam but also stiripentol, also a C219 inhibitor. If on both, the enzyme appears maximally inhibited meaning no further increase in, *N*-desmethylclobazam when CBD is addedlevels (Devinsky et al., 2018b).

4. Clinical Studies of CBD

4.1. Efficacy

The vast majority of studies have used an oral formulation of near pure CBD in sesame oil (<0.1%THC), manufactured by the UK company GWPharma, licensed in the US in 2018 and Europe in 2019 as Epidiolex™.

The publication of data from an early open label trial (expanded access program) in drug resistant patients with a range of etiologies in 2016 (Devinsky et al., 2016) was quickly followed by double blind studies in Dravet Syndrome (Devinsky et al., 2017), and Lennox Gastaut Syndrome (Devinsky et al., 2018a; Thiele et al., 2018). Together with more extensive open label data (Szaflarski et al., 2018), summarized in Table 1, this led to licensing for Dravet and Lennox Gasutaut Syndromes in the USA in 2018. All studies relied on diary data of countable (motor) seizures for the primary endpoint, with a 4 week pre CBD baseline without other treatment changes.

TABLE 1 Open and blinded trials of CBD in epilepsy

Study, design	Condition (n, n)	Age (years)	Median Current, previous AEDs (range)	Duration efficacy phase (weeks)	Target Dose (mg/kg)	% RR CBD vs Placebo (SF)	%Withdrawals due to AEs, CBD vs Placebo
Double Blind Randomized Controlled Trials							
(Devinsky et al., 2017)	Dravet 61, 59	2-18	3 (1-5), 4 (0-26)	14	20	43 vs 27 (5 vs 0)	13 vs 1.4
(Devinsky et al., 2018b)	Dravet 27, 7	4-11	2.6 (1-4),	4 ^a	5-20	NA	2 vs 0

(Devinsky et al., 2018a)	LGS (AtS) 76,73	2-55	3 (1-5), 6 (0-22)	14	10 or 20	42 vs 37	13 vs 1.3
(Thiele et al., 2018)	LGS 86, 85	2-55	3 (1-5), 6 (0-28)	14	20	44 vs 20	14 vs 1.2
Open label prospective studies (including expanded access programs)							
(Devinsky et al., 2016)	TRE 162	1-30	3 (0-7), 3 (1-7)	12	25-50	39 (5)	7
(Szaflarski et al., 2018)	TRE 607	0.4-62	3 (0-10) NS	12-96 ^b	10-50	52	5
(Sands et al., 2019)	TRE 26	1-17	2 (0-3) 7 (4-11)	26 - 212	25	27 (8)	4

Table 1 legend: n,n = number on active treatment, n on placebo; AtS = atonic/drop seizures; RR = Responder rate (%)m defined as >50% reduction in motor seizure frequency. In the Dravets study this was Convulsive seizures; in the first LGS study Atonic (drop) seizures); SF = seizure free (if any). AE = Adverse events; SAE = serious adverse events. NA = not applicable; ^aThis was a dose-ranging safety study ^bEfficacy sustained over up to 96 weeks. Safety data based on f/u range 2 – 146 weeks. TRE=treatment resistant epilepsy. NS Not stated.

This totals 550 patients with Dravet or Lennox-Gaustaut syndromes in Randomized trials, and over a 1000 in open label studies of a range of etiologies. The majority of participants are children, mean age between 7-14 years, but ranging from the first year of life into late adulthood. Based on the RCT data, a recent systematic review (Elliott et al., 2019) found a significant reduction in the median frequency of monthly seizures with CBD compared with placebo (-19.8%, 95% confidence interval [CI] = -27% to -12.6%), and an increase in the number of participants (48%) with at least a 50% reduction in seizures (relative risk [RR] = 1.76, 95% CI 1.07-2.88). There have been high profile cases in the media of dramatic responses (Gayle, 2018); “emotional testimony” and selected case videos were submitted alongside the trial data to the US licensing authorities (Dyer, 2018). Reductions in severe seizure types, including tonic clonic, tonic and atonic seizure were seen as particularly beneficial. However, a recent systematic review concluded there was no significant difference in seizure freedom rates between CBD and placebo (relative risk [RR] = 6.77, 95% confidence interval [CI] 0.36-128.38), nor quality of life (mean difference 0.6, 95% CI = -2.6 to 3.9).

Another comprehensive review, pooling RCTs and open studies, estimated a number needed to treat of 8.3 for 1 to have a greater than 50% reduction in seizures, and likely seizure freedom rates of less than 1 in 171 exposed (Stockings et al., 2018). There are of course problems with open label observational data. Studies with highest risk of bias methodologically were the most likely to report better outcomes (Stockings et al., 2018). The role of the placebo response is of particular importance in this context, given the intense social and traditional media attention, as well as the strong belief held by many that a natural product is inherently safer and more effective than licensed pharmaceutical agents (O'Connell et al., 2017). Furthermore in some sites access to the EAP was dependent on seizure diary data, so baseline over-reporting can't be excluded. Two phase II studies in adults with focal epilepsy have also failed to demonstrate efficacy, one of transdermal CBD (O'brien et al., 2019) , and another of Cannabidaverin (Bialer et al., 2018). Nonetheless, the evidence supports that CBD can be effective, including in notoriously drug resistant paediatric syndromes for which there are relatively few licensed alternatives.

4.2. Tolerability

Epidiolex™ is licensed for up to 20mg/kg/day (usually split in two doses), but doses of 20-25mg/kg/day are used most commonly, limited by tolerability. Treatment related adverse events, mostly commonly including diarrhoea, reduced appetite, vomiting, abnormal liver function tests and somnolence are

common, and will affect up to 1 in 3 (Stockings et al., 2018). Symptoms are however often mild, improve over time or with dose reduction. Across the RCTs, drug withdrawals for adverse events occurred in 8.9% on CBD and 1.8% on placebo (RR = 5.59, 95% CI 1.87-16.73) (Lattanzi et al., 2018). There is a clear dose response with the corresponding RRs for CBD being 1.66 (95% CI 0.22-12.86) at 10mg/kg/day, and 6.89 (95% CI 2.28-20.80) at 20mg/kg/day (Lattanzi et al., 2018). Status epilepticus and SUDEP are also not uncommon (5-10%), but none thus far attributed to treatment, and most likely reflect the patient population. Overall, including RCTs and open label data 1 in 23 (2.2%) (Stockings et al., 2018; Thomas and Cunningham, 2018) experience serious side effects such as extreme somnolence (risking aspiration, postural difficulties, falls), severe diarrhoea (risking skin breakdown), or abnormal (>3 times normal limits) liver function tests. The US Licensing authorities (Buracchio et al., 2018) drew reference to the infection rate – 4% of in those on treatment (0% placebo), with the pneumonia risk notably 9.1 times higher in those receiving CBD (Thomas and Cunningham, 2018). Drug interactions with valproate (increasing the risk of hepatotoxicity) and clobazam (contributing to somnolence, increased secretions and probably risk of chest infections as well as potentially efficacy) are also currently recognized, though can often be managed with dose changes (De Caro et al., 2017). On this basis, close clinical and laboratory monitoring, particularly during titration is recommended.

CBD is traditionally viewed as not sharing the risks of dependence seen with recreational cannabis, with some also arguing that high CBD offsets any theoretical risk from THC in formulations containing both (Huestis, 2007). Studies in which administration of single dose (750mg) to a highly sensitive population of recreational polydrug users showed no significant or consistent abuse potential (Bialer et al., 2018). However, there were subjective effects at higher doses. Of more concern, though as yet only published in abstract form (Uliel-Sibony et al., 2018), is a prospective study of 92 consecutive patients with treatment resistant epilepsies (mean age 11.8 years, range 1-37), receiving a 20:1 CBD/THC formulation followed for an average of 19.8 months. Tolerance, defined as needing a 30% or more increase in dose following reduction of efficacy, or a response reduction of more than 30%, was seen in 32.6% of patients. The robustness of this finding, and whether it might also apply to pure CBD formulations remains to be determined.

5. Place of CBD in clinical practice

Unsurprisingly, as remains the case for most of our licensed adjunctive treatments in treatment resistant epilepsy, there are no comparative studies against other AEDs. Limitations in current trial designs are also increasingly recognized, including their reliance on seizure diaries, strict inclusion/exclusion criteria and short durations which may fail to adequately account for the inherent variability of treatment resistant epilepsies (Shorvon and Schmidt, 2016). The best indicators for indirect comparisons is also debated – with clinicians often favouring number needed to treat (or harm), licensing authorities requiring responder rates or % reduction in seizures, and statisticians arguing for odds ratios (Lesaffre et al., 2000). As discussed earlier, assuming a NNT of 8 for 1 to benefit, and a 48% responder rate, as a broad comparison the NNTs for other recently licensed AEDs average around 10 (range 10-19), with responder rates mostly in the 30-40% range (Costa et al., 2011). Withdrawals due to adverse events were typically around 10% (5-15), and the number needed to harm around 25 (10-26) (Costa et al., 2011) (Costa et al., 2011) (Costa et al., 2011). One year retention rates for CBD appear very favourable at up to 76% (Szaflarski et al., 2018) compared for example to 65% for levetiracetam in early studies (Bootsma et al., 2008), but may be not insignificantly influenced by the cultural attachment to the idea of cannabis derived products as a “non-drug” option (Press et al., 2015). Whilst there may be beneficial effects of CBD on mood, social function and other comorbidities that drive retention, even without improved seizure control (Rosenberg et al., 2017) this is also the case for many other well established antiepileptic drugs. CBD isn't thus strikingly different on current evidence – effective for some and sometimes well tolerated

yes, potentially useful in severe drug resistant cases certainly, but the magic answer for most people with drug resistant epilepsy, clearly not.

6. Products containing THC

Almost all of the available data for THC containing products relates to artisanal formulations, other than one small recent study of a pharmaceutical grade CBD:THC 50:1 formulation in 20 children with Dravet syndrome (McCoy et al., 2018).

All are open label, so vulnerable to the same bias as open label/expanded access programs for pharmaceutical products. Marketing and product labelling also sometimes suggest better tolerability or even synergist potency for CBD:THC combinations, which whilst biologically plausible, together with conscious and unconscious bias against Pharma, implies potentially even greater selection bias. The role of the placebo effect, which appears to be strong in epilepsy trials (Goldenholz et al., 2015), may also be particularly pertinent to medicinal cannabis use. Patients with intellectual disabilities and severe epilepsy (Zaccara et al., 2015) may be particularly liable to a placebo response, and a two-fold greater placebo response in children compared to adults (Rheims et al., 2008) has also been reported. In the context of intense media coverage of specific cases and community advocacy leading to high expectations in some parents, that a 40% placebo response was been reported (Schultz, 2018), is perhaps not that surprising.

Some (Pamplona et al., 2018), not dissuaded by the low quality of available data, have applied meta-analysis techniques to purely observational data. Based on 670 patients, in 11 of the better-quality studies they concluded that CBD-rich extracts seemed to present a better therapeutic profile than purified CBD. There was similar effectiveness (50% or greater reduction in seizures seen in 42% on CBD, and 38% on CBD-rich (THC containing) extracts, but higher reported improvement overall, and better tolerability. The authors further speculate that the CBD might block some of the adverse effects of THC. However the observed differences, even if real, could equally be attributed to dose effects and selection bias, with CBD doses in the pure formulations being higher (22-37mg/kg/day) than in the CBD rich THC containing (3.2 – 10mg/kg/day). In contrast, a review of 10 of the same observational studies of CBD:THC preparations (Stockings et al., 2018), 4 predominantly CBD, and 6 using Sativex™ (1:1), in all instances as adjuvant treatment, with up to 7 years of follow up data, concluded there is insufficient evidence to draw firm conclusions on whether THC is of any added benefit (or harm) in epilepsy over and above that of CBD.

A further not insignificant issue in relation to artisanal products is the considerable variability in content, and labelling accuracy. Studies of products from US dispensaries (Vandrey et al., 2015) or online (Bonn-Miller et al., 2017), suggest only a minority (17% , 31% respectively) are accurate to within 10% of stated CBD/THC content. Both under- and over-labelling were found. Whilst THC content is generally low, levels up to 6.45mg/ml were found in some, sufficient to produce intoxication or impairment, especially in children. Similarly, an Australian study analysed 51 products used by 41 families, and found that most of the products, contrary to expectation, contained low CBD concentrations (mean 1.38 +/- 4.2 mg/kg/day (range 0-20.8), with only 6% approaching the minimum doses used in clinical trials (10mg/kg/day) (Suraev et al., 2018). In contrast THC or metabolites were present in almost all (98%), mostly at low levels, though with very high urinary THC metabolites found in 2 children. There were no clear differences in CBD:THC profile in products perceived as “effective” or “ineffective”. As also seen on many case reports and observational studies, families also reported benefits on cognition, wellbeing, language, sleep and behaviour – though no significant differences in formal assessments were found between children using CBD extracts compared to 24 families who had not. As we will go on to discuss, exposing particularly young developing brains to THC may well deliver perceived “benefits” at the time, but is not without risks.

6.1. THC associated risks

Dependence is estimated to affect around 9% of recreational cannabis users (compared to 14% for alcohol, and 32% for tobacco (Nutt et al., 2007)), and might explain some anecdotal reports of worsening seizures when cannabis preparations are discontinued. However, the bigger concern relates to possible adverse effects. Although most recreational cannabis users do not have associated problems, a substantial subset (10-30%) experience symptoms and consequences of a “Cannabis use disorder”(Budney et al., 2019). Compared with non-users, non-intoxicated cannabis users perform worse on measures of executive function, attention, learning and memory, motor skills and verbal abilities (Volkow et al., 2016). Whilst the effective size is modest (around 1/3 of the standard deviation), and there is no discernible difference after 1 month of abstinence, both magnitude and persistence are likely influenced by age, frequency and duration of exposure. The endocannabinoid system is present from the beginning of central nervous system development, around day 16 of human gestation, and is increasingly thought to play a role in neurodevelopment, including in relation to neurogenesis, neuronal migration, dendrite and axonal pathfinding (Volkow et al., 2017). Thus younger brains, at least up to adolescence, may be especially vulnerable to adverse effects from substances interfering with this system, and multiple basic and clinical laboratories have demonstrated potentially harmful effects (Budney et al., 2019). Neuroimaging studies suggest possible decreased connectivity and altered function, as well as potentially irreversible structural changes (Lorenzetti et al., 2019). Although separating cause and consequence is challenging, and at least some findings likely reflect structural markers of liability to addiction, accumulating clinical evidence supports that earlier exposure to cannabis is associated with greater impairment, including in longitudinal studies (reviewed in (Volkow et al., 2016)). A consistent association between adolescent cannabis use and later risk of psychosis is also recognized, accounting for 8-14% of cases of schizophrenia. To what extent this is causal, and the magnitude of any effect remains a subject of debate (Hamilton and Monaghan, 2019), but is of sufficient concern, together with emerging evidence of similar but small effects in mania and suicide to support public health education efforts (Sideli et al.). People with epilepsy, and in particular adults and children with early onset developmental epileptic encephalopathies and other severe drug resistant epilepsies, are already vulnerable to psychiatric and cognitive disorders (Mula and Cock, 2014). Only CBD has been well studied in clinical epilepsy trials thus far and ultimately we don't know if there is a “safe dose” of THC meaning on current evidence it is difficult to recommend preparations including THC.

7. Legislation, licensing and supply

Cannabis use for recreational purposes is still prohibited in most countries, though several now tolerate possession and personal use. Similarly, an increasing number of countries and US states now support the use of cannabis derived products for medicinal purposes. Hemp-derived CBD is legal in all 50 US states, and products labelled as less than 0.2% THC are widely available internationally often promoted as health supplements (Thomas and Cunningham, 2018). One pharmaceutical preparation of CBD for epilepsy is now licensed in the US, likely extended to Europe in 2019 (Torjesen, 2018), but limited to those with drug resistant Dravet or Lennox Gastaut syndromes. Epilepsy clinicians thus now face an unprecedented situation in which many individuals wishing to try cannabinoids as a treatment for their or their child's epilepsy can access this more readily over the counter than on prescription. Despite the uncertainties about composition, effectiveness, risk, and sometimes not inconsiderable costs (better quality artisanal preparations can still cost EUR10,000's/year (2018)) self-administered cannabinoid use for epilepsy is becoming increasingly prevalent. Up to 15% of adults, and 13% of parents/guardians of children with epilepsy reported using cannabis products at some point in a recent Australian Study (Suraev et al., 2017). In a follow up study of 41 families, only 76% had disclosed this to their treating doctors (Suraev et al., 2018).

8. Conclusions

The landscape for people with epilepsy and those treating them is indeed changing. Preclinical and clinical data supports that Cannabidiol offers new hope for patients with drug resistant motor seizures in Dravet and Lennox Gastaut syndromes, and possibly in a broader range of drug resistant epilepsies. It is not however a “game changer” based on current evidence in terms of efficacy or tolerability, and there is much still to be learnt. There are justifiable concerns about the use of THC containing products, particularly in children and adolescents. The biggest change however relates to the widespread availability of non-pharmaceutical formulations of a newly licensed drug for epilepsy, and shifting public attitudes to medicinal cannabis, pharmaceutical companies and medicine. Clinicians (personal experience of both authors) are increasingly pressurized to consider cannabinoids in preference to other licensed agents that have a much better evidence base, and are sometimes perceived as prioritising costs over patient choice and welfare, by apparently denying access to a potentially beneficial treatment. In parallel, clinicians have been criticised for failing to adequately inform patients of potential risks in relation to valproate and pregnancy, leading to now stringent recommendations about ensuring truly informed consent, and appropriate preventative strategies (Watkins et al., 2019). Sometimes conflicting beliefs in relation to cannabis and epilepsy, and more broadly, pose substantial challenges for both those living with, and supporting people with epilepsy as well as legislators and regulators. Continued education of the public, policymakers, researchers and healthcare providers about what is and isn't yet known, together with on-going good quality research is essential to mitigate against future potential risks, particularly in relation to vulnerable populations.

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Cannabidiol

1

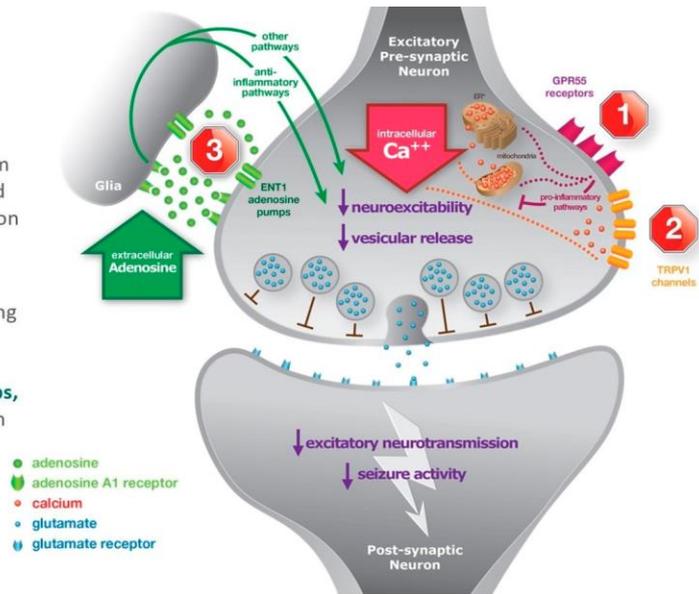
Antagonises GPR55 receptors, reducing calcium release from intracellular calcium stores and decreasing calcium levels¹ and potentially modulating neuroinflammation

2

Desensitizes TRPV1 channels, reducing extracellular calcium influx and decreasing calcium levels²

3

Inhibits ENT1 adenosine reuptake pumps, increasing extracellular adenosine, which reduces neuroexcitability and neurotransmitter vesicular release via anti-inflammatory and other signaling pathways³



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Figure 1 . Proposed multimodal mechanisms of action of cannabidiol reduce neuroexcitability

With permission from Greenwich Biosciences, Inc. Ca⁺⁺, calcium; ENT1, equilibrative nucleoside transporter 1; ER*, endoplasmic reticulum; GPR55, g-protein-coupled receptor 55; TRPV1, transient receptor potential vanilloid 1. ¹(Bazelot et al., 2018) ²(Jones et al., 2018) ³(Carrier et al., 2006)