Epilepsy and cannabis – “so near, yet so far”

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Abstract: Following media attention on children with refractory epilepsies reportedly deriving benefit from cannabis based medicinal products (CBMPs), the UK government changed the law in 2018 so that CBMPs could be legally prescribed. Subsequently, a pure cannabidiol product has been licensed in two epilepsy syndromes. However, despite pressure from campaign groups and allied politicians, almost no children have received unlicensed CBMPs under the UK National Health Service.

This review explores the science behind CBMPs in paediatric epilepsies and highlights the areas that warrant further research. It identifies a lack of level one evidence for efficacy and safety as currently the major obstacle to prescribing. Unlicensed medicines are often used in paediatrics but almost all are used "off-label", with supporting evidence of efficacy and safety derived either from other age-groups or from disease conditions. CBMPs, excepting pure cannabidiol, are unique in that they are currently both unlicensed and fall outside the "off-label" category.

The review acknowledges the treatment gap in refractory epilepsies and the potential for CBMPs. However, it argues against exceptionally circumventing the usual standard of evidence required by regulatory prescribing authorities and warns against allowing vulnerable children to become the trojan horse for deregulation of the commercial cannabis market.

What this paper adds

• Unlicensed CBMPs should not circumvent usual regulatory requirements before widespread prescription.

• Children with epilepsy are at risk of being used as the trojan horse for the cannabis industry.

In November 2018, United Kingdom law changed so that clinicians on the GMC Specialist Register were permitted to prescribe cannabis-based medicinal products (CBMPs). The change in the law was prompted by publicity surrounding high-profile cases of children with refractory epilepsy who had accessed CBMPs abroad, were reportedly deriving benefit and had then had the medicines confiscated by customs authorities on return to the UK. It was a striking example of "manufactured scandal" driving policy reform(1). In the House of Commons, the then Home Secretary, Sajid Javid had said: "The position we find ourselves in is not satisfactory. It is not satisfactory for the parents, it is not satisfactory for the doctors, and it is not satisfactory for me". Despite the subsequent change in the law, barely a handful of children and young people with epilepsy have received prescriptions for unlicensed CBMPs within the National Health Service in the United Kingdom, although a small number of prescriptions have been issued by physicians in private practice. How has it come to this? A substantial proportion of our media, politicians, and perhaps the families of our patients, also struggle to understand why we are in this position.

Cannabis has been used as a medicine for thousands of years. In UK medicine it achieved some acceptance in the 19th Century thanks to the efforts of William Brooke O'Shaughnessy an Irish Physician who worked for the East India Company. He described the therapeutic effects of cannabis indica in a variety of clinical scenarios including tetanus, rabies and an infant with convulsions(2). John Russell Reynolds, a prominent neurologist at Queen's Square and President of the Royal College of Physicians, was also an advocate of cannabis for the treatment of migraine, neuritis and parasomnias. He was less enthusiastic about its use in epilepsy, noting in The Lancet that "in true, chronic epilepsy, I have found it absolutely useless, and this is the result of very extensive experience"(3). Famously, in 1890, he prescribed it to Queen Victoria for the relief of menstrual cramps. William Gowers, in his treatise on Epilepsy and other chronic convulsive diseases, had a more considered view describing cannabis indica as being "sometimes, though not very frequently, useful" as a treatment for epilepsy(4). However, during the 20th century CBMPs fell out of vogue, partly because there was a move away from whole plant treatments as the ability to isolate individual molecules from plants increased and partly for legal reasons because cannabis was considered a drug of misuse.

The situation with respect to CBMPs has changed dramatically in the 21st century. There are still many chronic medical conditions that have few effective treatments. One third of our patients with epilepsy do not respond to current anti-seizure medications. These patients and their families are understandably eager to try any treatment that may improve their condition. Some high-profile cases have suggested that CBMPs may be the answer. In the US, one young girl with Dravet syndrome, started taking a cannabis oil known as "Hippie's Disappointment" and later renamed "Charlotte's Web" that apparently dramatically reduced her seizures. In the UK there have been similar cases that have suggested the benefits of CBMPs.

These cases coincided with the commercial interests of a growing medicinal and recreational cannabis market in the UK that is predicted to be worth $55 billion globally by 2027(5). Campaign groups, such as End Our Pain, closely connected to politicians in the All-Party Parliamentary Group (APPG) for Medical Cannabis on Prescription and with links to the cannabis industry, began to press for the prescription of unlicensed CBMPs(6). They

found common cause with clinical enthusiasts for the use of whole plant cannabis, some of whom also had financial interests in a growing medicinal cannabis market and also with a small number of politicians, not involved with the APPG for Medical Cannabis on prescription, who had long lobbied for the legalisation of marijuana(7). Paediatric neurologists, imbued with the need to practice evidence-based medicine and wary of prescribing unlicensed medicines that had inadequate safety data, suddenly found themselves at odds with an array of vested interests and, most unfortunately, the families of patients who were keen to try anything that would alleviate the effects of their child's seizures.

What is cannabis?

There are two main types of cannabis plant that are used for medicinal purposes: cannabis sativa and cannabis indica. The two different plants originate from different geographical areas and may have varying amounts of different cannabinoids. Sometimes the sativa and indica strains will be hybridised. The plants contain over 140 cannabinoid compounds. The most plentiful cannabinoids are Tetrahydrocannabinol (THC) and Cannabidiol (CBD) and almost all clinical research has focussed on them. THC is responsible for most of the psychoactive effects of cannabis. Plants can be cultivated to contain greater or lesser amounts of these two cannabinoids.

Humans produce endogenous cannabinoids, anandamide and 2-arachidonylglycerol, that are key modulators of synaptic transmission. They play a role in the regulation of feeding behaviour, perception of pain and the neural generation of motivation and pleasure. THC and CBD interact with the human endocannabinoid system and, in particular, the cannabinoid receptors CB1R and CB2R. CB1 receptors are predominately expressed in the central nervous system in microglia, astrocytes and oligodendrocytes and are found in high density in the hippocampus, brain stem, globus pallidus and middle frontal gyrus. They are also found in the myocardium. CB2 receptors are found predominantly in the immune system and gastrointestinal tract, although there is evidence that they are also present in the CNS but less abundantly than CB1 receptors(8). THC acts as a partial agonist of CB1 receptors inhibiting release of GABA and glutamate. The mechanisms of action of CBD are less clear but it appears to prevent other agonists from binding to CB1 receptors, acts as an agonist at serotonin and dopamine receptors, blocks voltage-gated sodium channels and inhibits the enzyme fatty acid amide hydrolase (FAAH) that breaks down endogenous cannabinoids(9). A review found evidence of CBD binding to in excess of 65 molecular targets(10). Both THC and CBD interact with transient receptor potential (TRP) ion channels that are involved in the transduction of chemical and physical stimuli(11).

In animal models, CBD has been shown to have anti-convulsive effects across a series of different models(12). THC has been seen to be both pro and anticonvulsant in animal models and the proconvulsant effects have been passed on to future generations(13, 14).

There has been long-standing concern about the adverse effects of THC exposure. Adolescent cannabis use, with varying, uncontrolled amounts of THC showed clear dose-response relationships with adverse young adult outcomes. These effects included reduced

odds of high-school completion and degree attainment with increased odds of later cannabis dependence, use of other illicit drugs and suicide attempts (15, 16).

There is some evidence that CBD may off-set some of the negative effects of THC. In a series of elegant experiments Englund et al. demonstrated how CBD can reduce some of the psychotic symptoms, paranoia and memory impairment induced by THC administration(17).

Dose-response and drug-drug interaction information for the cannabinoids is scarce. However, CYP2C19 converts N-desmethylclobazam to its inactive metabolite(18) and CBD is a potent inhibitor of Cytochrome P450 2C19 enzymes. Consequently, CBD significantly increases circulating levels of more sedating N-desmethylclobazam in patients taking clobazam.

The cannabis plants also contain terpenes. Terpenes are aromatic hydrocarbons and are often responsible for the characteristic scent we associate with many plants such as pine, lavender, oranges and lemons, and cannabis(19). The most abundant terpene in cannabis is myrcene, although there are many other terpenes present and the terpene profile may vary in different plants. A widely discussed issue is whether the terpenes add any therapeutic benefit, contributing to the so-called entourage effect of "whole plant" medicines. The concept is that all the constituents of the plant work in concert to create "the sum of all the parts that leads to the magic or power of cannabis". Although commonly referred to, there is little or no robust evidence to support the entourage effect as a credible clinical concept(20).

Evidence in paediatric epilepsy:

The recent NICE guideline on cannabis based medicines (NG144) was unable to make a recommendation on the use of CBMPs in refractory epilepsies acknowledging that "current research is limited and of low quality, making it difficult to assess just how effective these medicines are for people with epilepsy"(21) The only high quality level one evidence that has been published are double-blind randomised placebo-controlled trials of a pure CBD product, Epidyolex ®, in Dravet Syndrome, Lennox-Gastaut Syndrome and tuberous sclerosis complex(22-25). Trials in all three scenarios showed a significant benefit of CBD versus placebo at doses ranging from 10-20 mg/kg/day in the Dravet Syndrome and Lennox-Gastaut Syndrome trials and from 25-50 mg/kg/day in the tuberous sclerosis complex trial. In all the trials the lower dosing regimes appeared as effective as the higher dose regimes and the CBD was more effective in those patients concurrently taking clobazam. Patients rarely became seizure free on CBD with the median percentage reduction in seizure frequency varied between 38-48%. There was a significant placebo effect in these trials with patients on placebo having a median % reduction in seizure frequency between 14-27%. Sedation, diarrhoea and loss of appetite were common adverse effects. Some adverse effects related to concomitant clobazam use and transient liver enzyme abnormalities were seen in some patients receiving valproate. The efficacy of Epidyolex against multiple seizure types and in multiple underlying aetiologies in the Lennox-Gastaut syndrome trials suggests that pure CBD may have efficacy across the range of epilepsies. However, it has only been trialled and therefore licensed in these very narrow and circumscribed diagnostic groups.

There have been several open-label non-randomised non-controlled studies of CBD (Epidyolex ®) used in other clinical scenarios i.e. treatment resistant epilepsies in general, CDKL5 disorder, Doose syndrome, Aicardi syndrome, duplication of 15q, tuberous sclerosis complex and FIRES syndrome(26-28) ((29)-33). All these studies suggest that CBD is effective as an anti-epileptic medication, but all are vulnerable to bias due to their uncontrolled designs.

There has been a phase-2 open label study of another oral cannabidiol formulation in paediatric refractory epilepsy. The study looked at 16 children with refractory epilepsy of whom 11 completed the study. A highly purified cannabis sativa extract, containing greater than 93% cannabidiol and less than 0.2% THC, was delivered on gelatin beads. The maximum dose of CBD was 25 mg/kg/day. The mean reduction in monthly seizure frequency was 73.4%. 9 out of 16 patients were classified as responders(30).

Studies of CBMPs containing both CBD and THC in paediatric epilepsies are scarce and there is no level 1 evidence. McCoy et al. published the results from a prospective open-label trial of a CBD/THC cannabis oil in children with Dravet syndrome. 20 patients were recruited and 19 were analysed at the end of the study. One patient died during the course of the study and was not included in the final analysis. Patients were treated for 20 weeks with a product containing 100 mg/ml CBD and 2 mg/ml THC. They started at a dose of 2mg/kg/day of CBD and 0.04 mg/kg/day of THC and were titrated up to either 16 mg/kg/day of CBD and 0.32 mg/kg/day of THC or the maximally tolerated dose. The maximum target dose was reached by 8 of the 19 participants. Seizure frequency at the end of the study was compared to baseline and 12 children had a greater than 50% reduction in seizure rate and there was a 70.6 median percentage reduction in motor seizures(31).

Prospective and retrospective open-label cohort studies of both children and adults of a whole-plant CBMP product cultivated to have a CBD/THC ratio of 20:1 have been published from Israel. These studies have shown that the CBMP was associated with a > 50% reduction in mean monthly seizure frequency in 51-56% of patients(32-34). In addition to these studies there have been numerous open-label reports of the apparent effectiveness of a variety of different CBMPs in paediatric and adult epilepsies.

Levels of evidence:

In the vast majority of cases medicines regulatory authorities require level 1 evidence (i.e. randomised controlled trials) of efficacy and safety before licensing any new medicine. Unfortunately, apart from the studies of pure cannabidiol in Lennox-Gastaut and Dravet syndromes and tuberous sclerosis complex, level 1 evidence in the field of CBMPs and refractory epilepsy is lacking. Some have argued that reliance on Level 1 evidence to make decisions about licensing and prescribing is misplaced. Professor David Nutt in an opinion piece for the BMJ argued that in the case of CBMPs we should accept a lower standard of evidence such as patient-reported outcomes, observational research, and n of 1 trials. He also argues that there are already many examples of drugs licensed without RCT evidence(35). In reality such licensing is relatively rare and almost always occurs in the context of haematological malignancy, solid tumour oncology or metabolic conditions,

where no effective treatment alternative is available or where the drug is so obviously effective that clinical equipoise no longer exists(36). This is not the scenario with CBMPs. The problem with lesser standards of evidence is that they are vulnerable to bias. Open label studies of drugs almost invariably exaggerate the benefits of medicines. In his evidence to the UK Parliament Health and Social Care Committee inquiry "Drugs Policy: Medicinal Cannabis", the Chief Scientific Adviser to the Department of Health and Social Care (and now Chief Medical Officer) Professor Chris Whitty argued that CBMPs should be subject to the same level of scrutiny as other drugs and that "… it is very dangerous to have a kind of cannabis exceptionalism". The Health and Social Care Committee in its conclusions to the inquiry noted that: "Some have argued that double blind RCTs are inappropriate for cannabis research but we do not support making an exemption for this class of medicines". The committee also exhorted the CBMP manufacturers to put forward their products for research(37). With the exception of the manufacturers of Epidyolex ®, they have conspicuously failed to do this.

One of the problems with open-label studies is that they fail to account for the placebo effect. The placebo effect is a real phenomenon and appears especially potent in the context of CBMPs. In the randomised controlled trial of cannabidiol in Dravet syndrome, for example, 27% of patients on placebo had a 50% reduction in seizure frequency and 34% of patients had an improvement on the care-giver impression of change(22). Another example of the potency of the placebo effect is a study from Colorado where the law restricting the use of cannabis products is relatively relaxed. In a single tertiary epilepsy centre they compared the epilepsy responder rates to a cannabinoid treatment between children of families resident in Colorado compared to those who had moved to Colorado in order to access cannabinoid treatment for their child's epilepsy. The responder rate for Colorado resident children was 22% but rose to 47% for those families who have moved into the state(38). A plausible interpretation of these results is that this is a "placebo by proxy" effect(39).

The Prescribing environment

The change of law in November 2018 permitted access to a CBMP in one of three ways: as a medicine with a marketing authorisation, as part of a clinical trial or through the prescription by "senior clinicians" in cases of "exceptional clinical need". The Departments of Health of the four nations of the UK noted that a senior clinician's decision to prescribe should take account of General Medical Council (GMC) guidance, have approval by the clinician's local employer and have that decision to prescribe peer-reviewed. The GMC is the regulatory body for doctors in the UK and its guidance clearly states that a clinician "must be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy". Perhaps, given the standard of evidence that exists around CBMPs in paediatric epilepsy, it is not surprising that many senior clinicians are not sufficiently reassured to prescribe.

The unlicensed status of CBMPs is peculiarly unique. In UK hospital practice up to 40% of medicines used for children are "unlicensed" and in recent years the European Medicines Agency has attempted to address this(40). However, almost all of drugs prescribed in this way are prescribed "off-label" such that they have an existing license, either for an older age

group or for an alternative medical indication. In paediatric epilepsy practice, perhaps with the sole of exception of rarely used potassium bromide, the potential prescription of a CBMP would fall outside an off-label definition. It follows that there will have been no regulated trial efficacy or safety data on which to rely.

Furthermore, approval for the funding of unlicensed medication needs to be obtained via individual funding requests from NHS local "Drugs and Therapeutics Committees". In the light of the lack of evidence of efficacy and safety, together with their current costs, that approval has rarely been forthcoming.

Legislation in different countries

Internationally, there is considerable variation in whether cannabis is permitted to be used in different countries. In recent review, it is noted that the use of herbal cannabis for medicinal purposes is permitted in Argentina, Australia, Canada, Chile, Colombia, Croatia, Ecuador, Cyprus, Germany, Greece, Israel, Italy, Jamaica, Lithuania, Luxembourg, North Macedonia, Norway, the Netherlands, New Zealand, Peru, Poland, Switzerland, and Thailand, as well as a number of states in the USA.(41) However, outside pure cannabidiol, there has been no approval for cannabinoid products for the treatment of epilepsy by either the European Medicines Agency or the US Food and Drugs Administration.

In Canada, by 2019, some 165 cannabis producers were licensed to sell cannabis products to authorised medical patients – although pure cannabidiol was unavailable at that time. That same year, the Canadian League Against Epilepsy Medical Therapeutics Committee produced a guarded position statement highlighting, again with exception of pure cannabidiol in published RCTs, the lack of evidence for the efficacy and safety of cannabis medicines for children with epilepsy. (42).

Conclusions

CBMPs hold promise for the treatment of refractory paediatric epilepsies. There is historical and low-level clinical data suggesting the possible efficacy of these treatments. However, there is no reason why CBMPs should be exempt from the same efficacy and safety trials required of most other pharmaceutical products in medical practice. This requires properly designed and conducted RCTs. There should also be further trials to evaluate the use of pure cannabidiol beyond the limited number of syndromes for which it is currently licensed. Such an approach must be to the benefit of our patients. Furthermore, on behalf of our patients, the UK government and its research and regulatory agencies spend millions of pounds annually ensuring that this level of evidence exists for other medicines.

All clinicians caring for children and young people with poorly controlled epilepsy recognise their plight and the wish of families to do the best for their child. There is a danger that vulnerable families will be unwittingly exploited by vested interests using children with poorly controlled epilepsy as a "Trojan horse" for deregulation of the cannabis market - the idea being that widespread acceptance of medicinal cannabis will preface and accelerate the wider legalisation of marijuana and open up a highly lucrative commercial market. Companies producing CBMPs should not be allowed to circumvent the usual standards of

evidence required by regulatory authorities and they should be called to account if they will not participate in randomised controlled trials. We need carefully designed, good quality CBMP studies that produce results on which we can rely. We can then work with families to choose the best treatments for children and young people with epilepsy. We owe this to them.

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