

# **Commentary and critique on the BNPA publication:**

Guidance on the use of  
cannabis-based products  
for medicinal use in children  
and young people with  
epilepsy (Oct 2021)

By the  
Medical Cannabis Clinicians Society &  
Drug Science

## About this document

This document by the Medical Cannabis Clinicians Society (MCCS) and Drug Science offers a critique of the guidance produced in October 2021 by the British Paediatric Neurology Association.

The MCCS and Drug Science fundamentally differ with the BPNA with regard to their conclusions about the use of cannabis-based products for medicinal use (CBPMs).

## How to read this document

In this document we have quoted directly from the BPNA document (in black) and added our critique (green highlight).

[Link to original BPNA publication products for medicinal use \(CBPMs\).](#)

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# Glossary

<b>ACMD</b>	Advisory Committee on Misuse of Drugs
<b>ADR</b>	Adverse drug reaction
<b>ALT</b>	Alanine Aminotransferase
<b>AST</b>	Aspartate Aminotransferase
<b>BPNA</b>	British Paediatric Neurology Association
<b>CBD</b>	Cannabidiol
<b>CBPM</b>	Cannabis-based product for medicinal use
<b>EMA</b>	European Medicines Agency
<b>Full spectrum</b>	Full spectrum products – cannabis products containing all natural cannabinoids and terpenes in that chemovar, including variable amounts of THC
<b>GDP</b>	Good distribution practice
<b>GMC</b>	General Medical Council
<b>GMP</b>	Good manufacturing practice
<b>Isolate</b>	Isolate products – just contain 99.9% pure cannabinoid
<b>IMP</b>	Investigational medicinal product
<b>NICE</b>	National Institute of Clinical Excellence
<b>NHS</b>	National Health Service
<b>MHRA</b>	Medicines & Healthcare products Regulatory Agency
<b>RCT</b>	Randomised controlled trial
<b>THC</b>	Tetrahydrocannabinol
<b>MCCS</b>	Medical Cannabis Clinicians Society

## 1. Introduction

The British Paediatric Neurology Association (BPNA) was asked in 2018 by NHS England, and on behalf of the devolved nations, to develop interim clinical guidance for clinicians in the use and prescription of cannabis-based medicinal products (CBPMs) in children and young people with epilepsy. In November 2019 (last updated March 2021) the National Institute for Health and Care Excellence (NICE) published a guideline on cannabis-based medicinal products [NG144]. The NICE guideline covers prescribing of CBPMs for individuals with severe treatment-resistant epilepsy. Separately, NICE has published technology appraisal guidance on cannabidiol with clobazam for treating seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) and, therefore, the use of cannabidiol (CBD) for these syndromes was not considered in the NICE guideline [NG144].

This current guidance document has been produced at the request of our members and both reflects and complements the Cannabis-based medicinal products NICE guideline [NG144].

The Medical Cannabis Clinicians Society has also produced guidance on medical cannabis prescription, which the BPNA have ignored.

Latest update: [Recommendations-and-Guidance-on-Medical-Cannabis-under-Prescription-3rd-Edition-2021-reduc..pdf \(ukmccs.org\)](#)

## 2. Background

2.1 The previous Chief Medical Officer, Professor Dame Sally Davies produced a review of the therapeutic and medicinal benefits of cannabis-based products in June 2018<sup>1</sup>. On the basis of this review, she recommended that the whole class of cannabis-based medicinal products be moved out of Misuse of Drugs Regulations Schedule 1. This review looked at the use of cannabis-based products in a variety of different medical conditions, including epilepsy. Her review was based predominantly on four main sources:

2.1.1 The American National Academies of Sciences, Engineering and Medicine (USA) report on “The Current State of Evidence and Recommendations for Research Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda, 2017

2.1.2 The Health Products Regulatory Authority (Ireland) report on “Cannabis for Medical Use – A Scientific Review, 2017

2.1.3 World Health Organisation Expert Committee on Drug Dependence, 2018

2.1.4 The Australian Government Department of Health Therapeutic Goods Administration report on “Medicinal cannabis – guidance documents, 2018”<sup>2-9</sup>

These sources suggested that to date there was either insufficient evidence or limited evidence that cannabis-based products were of therapeutic benefit in epilepsy and specifically that good quality evidence was confined to the use of cannabidiol (CBD). These sources (now out of date) all ignore the overwhelming weight of positive evidence from non-RCT studies. There is considerable Real-World evidence of the efficacy and safety of CBPMs for epilepsy. The BPNA are stuck inappropriately in a pharmaceutical industry paradigm, in which CBPMs do not fit and never will.

### 2.1.5 Real world evidence v RCT evidence

The cannabis plant contains 147 cannabinoids and over 100 terpenes and flavonoids, as well other plant chemicals such as chlorophyll and waxes. These are not “contaminants” but an integral part of the plant and many of these components have medicinal value. As an example, there are at least nine cannabinoids and terpenes that are known to have anti-convulsant properties. The basis of the double-blind, placebo-controlled trial is to compare a single compound, usually pharmaceutical, product with a placebo. Occasionally, a multi-compound medicine can undergo such studies, such as Sativex which is a combination of THC and CBD. However, it is not possible to conduct such studies for full-spectrum cannabis because of the complexity of the medicine and of course the difficulty of an adequate placebo. Comparison of isolate cannabinoids is possible (such as the Epidyolex studies, as Epidyolex is “nearly” an isolate (it contains a small amount of THC)). If the full-spectrum product is more efficacious than the isolate products (as appears to be the case - section 3.5.1) then the inability to conduct RCTs will forever miss their benefits.

Sir Michael Rawlins in his Harveian Oration in 2008<sup>37</sup> stated that “Hierarchies of evidence should be replaced by accepting - indeed embracing - a diversity of approaches.....it is a plea to

investigators to continue to develop and improve their methodologies; to decision makers to avoid adopting entrenched positions about the nature of evidence and for both to accept that the interpretation of evidence requires judgement” “As Bradford Hill, the architect of the RCT, stated so cogently: “any belief that the controlled trial is the only way would mean not that the pendulum had swung too far but that it had come right off the hook””

Professor Rawlins rightly discusses the value of the historical controlled trial, the non-randomised controlled trial, the case-control study, the before-and-after designs as well as case series and even case reports. The evidence of efficacy for the use of cannabinoids in epilepsy using these reasonable approaches is substantial (see section 3.5.1).

- 2.2 The Advisory Committee on Misuse of Drugs (ACMD) gave advice to the Home Secretary on cannabis-based products for medicinal use (CBPM) and a summary of this advice is that<sup>10</sup>:
- 2.2.1 Products with a clear definition are moved out of the currently illegal Schedule 1 status into Schedule 2.
- 2.2.2 There should be an option to prescribe CBPMs that meet the requirements for medicinal standards.
- 2.2.3 There should be “checks & balances” to maintain safe prescribing and to avoid harm. These recommendations were accepted by the Home Secretary in July 2018<sup>11</sup>.
- 2.3 The following definition of a cannabis-based product for medicinal use (CBPM) has been formally agreed by the UK Government:
- 2.3.1 It contains cannabis, cannabis resin, cannabidiol or a cannabidiol derivative.
- 2.3.2 It is produced for medicinal use in humans.
- 2.3.3 It is:
- i. a medicinal product; or
  - ii. a substance or preparation for use as an ingredient of a medicinal product; or
  - iii. a substance for use in the preparation or manufacture of an ingredient of a medicinal product.
- 2.4 In January 2020 the UK Advisory Council on the Misuse of Drugs (ACMD) and its technical committee recommended to the Minister of State for Crime and Policing that Epidyolex (cannabidiol) be reclassified from a schedule 2 controlled drug to a schedule 5 controlled drug because of its low potential for misuse. This advice was accepted and the new provisions came into force in June 2020.
- 2.5 UK Government proposed prescribing framework:
- 2.5.1 Initiation of prescribing will be restricted to doctors on the Specialist Register, prescribing only within their relevant specialist registration.

To be clear, the framework also includes the provision for GPs, other doctors and

pharmacists to prescribe on follow-up after the initial prescription by the specialist doctor. The exact legal wording in the "The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018 is:

"in accordance with a prescription **or direction** (our emphasis) of a specialist medical practitioner";

The explanatory memorandum accompanying the legislation states that:

"That doctor will need to look to other sources of reassurance and ultimately, it will be for the specialist doctor, making the decision to prescribe, to decide whether prescribing these products is in **the best interest of the patient**"(our emphasis)

We note that it is the best interest of the patient and not in the best interest of the individual doctor or their specialist association.

2.5.2 There will be three access routes:

- Prescribing these products will be treated as "specials"; i.e., in the same way as an unlicensed medication
- As an investigational product in the context of a clinical trial
- As a medicinal product with a marketing authorisation

2.5.3 The assumption is that prescribing of unlicensed medicines is "a last resort" and "used only when no other drug with MHRA marketing authorisation meets the clinical need". The MCCS and Drug Science point out the helpful Frequently Asked Questions provided by NHS England:

NHS England » Cannabis-based products for medicinal use: Frequently asked questions

2.5.4 Responsibility remains with the prescribing clinician and not with the BPNA.

2.5.5 This UK Government guidance applies to both public and private sectors.

2.5.6 All CBPMs should have a clear contents description, and specifically including doses and concentrations of CBD and THC.

The MCCS and Drug Science would prefer a full Certificate of Analysis which should include not only THC and CBD information but a profile of minor cannabinoids and terpenes.

### 3. Summary of current knowledge

- 3.1 The BPNA has previously produced a public statement on the use of cannabis related products<sup>12</sup>. We briefly summarise below the issues around the two most investigated compounds, cannabidiol (CBD) and tetrahydrocannabinol (THC).
- 3.2 There is good quality clinical evidence that CBD has an anti-epileptic effect in three conditions that are characterised by severe epilepsy (Dravet Syndrome, Lennox-Gastaut Syndrome and Tuberous Sclerosis Complex) and evidence from open-label studies and animal studies that it is likely to have an anti-seizure effect in the epilepsies in general<sup>13-19</sup>. CBD has multiple molecular targets. CBD is a negative allosteric modulator at cannabinoid type 1 (CB1) receptors, a partial agonist of serotonin and dopamine receptors, blocks voltage-gated sodium channels and is an inhibitor of the enzyme Fatty Acid Amide Hydrolase (FAAH) that degrades endogenous cannabinoids. THC may also have an anti-epileptic effect, although some animal studies suggest that it can also have a pro-convulsant effects<sup>12</sup>. THC binds to the cannabinoid receptors, CB1 and CB2, in the brain and it is thought that the CB1 receptor binding is responsible for the psychoactive effect of cannabis.
- 3.3 There have been open-label and uncontrolled studies of cannabidiol (CBD) showing seizure reduction in epilepsy<sup>14,17,18,21</sup>. Since 2017, four double-blind, randomised controlled trials of pure CBD (Epidyolex ®) in Dravet syndrome, Lennox Gastaut syndrome and Tuberous Sclerosis Complex have been published<sup>13,15,19,20</sup>. The median monthly reduction in seizure frequency was significantly greater in patients randomised to CBD compared to patients on placebo (42% in patients on 20mg cannabidiol vs 17% in the placebo group). Similarly, there was a statistically significant greater than 50% reduction in 39% of patients on 20mg cannabidiol vs 14% in the placebo group. Sedation, diarrhoea and loss of appetite were common adverse effects, **although these side effects were in general mild and well tolerated.**
- 3.4 CBD has a series of drug interactions possibly in part because of its effect on the cytochrome P450 system. It is known to alter drug levels of benzodiazepines, rufinamide, topiramate, zonisamide, eslicarbazepine and perampanel. This is particularly the case for clobazam, where CBD administration significantly increases the levels of N-desmethylclobazam, the active metabolite of clobazam, and can result in increased clobazam side-effects. Raised AST and ALT levels are commonly seen in conjunction with sodium valproate use, but these usually settle over time<sup>22</sup>. **Assuming the prescribing doctor is aware of potential interactions, as properly trained cannabis physicians will be, then the risks of significant drug-drug interactions are usually minimal and easily managed.**
- 3.5 There are considerably fewer data on the effectiveness and safety of products containing THC in epilepsy in children and young people. Animal data show both anticonvulsant and proconvulsant properties of THC<sup>16</sup>. An open-label non-randomised study from Canada examined the use of the product TIL-TC150 – a cannabis plant extract produced by Tilray®, (containing 100mg/ml CBD and 2mg/ml THC) in twenty children with Dravet syndrome and has demonstrated some short-term safety and dosing data and some evidence of effectiveness<sup>23</sup>. However, the study was small, unblinded, had no control group and therefore does not



constitute high quality evidence of either effectiveness or safety. There have been two further open label non-randomised uncontrolled studies from Israel that have demonstrated efficacy of a medicinal cannabis oil plant extract that contained both CBD and THC in refractory epilepsy in children and adolescents. The patients were treated with a cannabis oil extract from plants cultivated to have a CBD/THC ratio of 20:1. In the first study 26/46 patients (56%) had a >50% reduction in mean monthly seizure frequency<sup>24</sup>. The second study was a retrospective analysis of a case-series of 74 patients and 38 patients were reported to have had a >50% reduction in seizures according to parental report at clinic visits<sup>25</sup>. Again, the studies are vulnerable to bias due to their uncontrolled designs.

The Canadian Childhood Cannabinoid Clinical Trials programme is running the Canadian Pediatric Surveillance Program which is a pharmacovigilance study. Over 2800 paediatricians have sent information over the last 2 years. They have received no notifications of serious adverse reactions to full-spectrum cannabis in any epileptic child. The total number of children with drug-resistant epilepsy and having a cannabis prescription in Canada is around 2000.

### 3.5.1 Epilepsy and cannabis studies

We think it is useful to summarise some of the emerging studies regarding full-spectrum cannabis products and childhood epilepsy. This is not a definitive review but may help interested clinicians come to a reasoned decision about prescribing such products.

In 2018 Pamplona and colleagues published a meta-analysis of CBD-rich cannabis extracts in comparison with purified CBD in treatment-resistant epilepsy. They found 11 valid references with a total of 670 patients. They found improvement in seizure frequency (to any extent) in both groups but more so in the CBD-rich extract group (71%) compared with the pure CBD group (36%) –  $p < 0.0001$ . The difference did not apply when the 50% seizure reduction threshold was used (38% v 42%). The mean dose in the CBD-rich group was 6.1mg/kg whereas it was 27.1mg/kg in the pure group. Therefore, the side effect profile was much preferable for both mild and severe side effects in the CBD-rich group. They felt that the CBD-rich extracts presented a better therapeutic profile than purified CBD, possibly due to the synergistic effects of other phytocompounds in the CBD-rich group (the so-called entourage effect)<sup>39</sup>

Tzadok and colleagues<sup>25</sup> produced similar results in a retrospective study of CBD-rich extract in 74 patients with intractable epilepsy. The patients had been resistant to more than 7 anti-convulsants and 66% had failed a ketogenic diet, Vagal Nerve Stimulation (VNS) or both. They used a 1:20 THC:CBD oil and 89% reported a reduction in seizures with 52% reporting more than 50% reduction. Five patients withdrew due to side effects including somnolence, gastrointestinal disturbance and irritability and seizure worsening although others (59%) reported improvements in behaviour, alertness, language, communication, motor skills and sleep.

In 2019 Huntsman and colleagues<sup>40</sup> published early result from the CARE-E study which was an open-label prospective dose-escalation trial using cannabis extract preparation of Health Canada approved 1:20 THC:CBD oil at 10-12mgs/kg CBD per day in children with drug-resistant epilepsy. All 7 participants had improvement in seizure frequency which was 74% at 10- 12mgs/kg per day and three children became seizure free. An improvement in cognitive, social and emotional

functioning (using QOLCE-55) was noted in all children. Side effects were experienced (such as nausea, diarrhoea, increased appetite, sleep problems and spasticity) but none were severe enough to withdraw from the trial. EEG rating scores also improved. They felt that the THC combination was probably more effective than purified CBD alone and felt that THC intoxication was unlikely at 1:20 ratio when CBD was used at 10-12mgs/kg dosage.

Another recent study assessed the use of 100mgs/ml CBD with 2mgs/ml THC in 20 patients with Dravet syndrome and reported a median reduction of 70.6% ( $p < 0.05$ ) in motor seizures as well as a reduction in EEG activity and quality of life improvements<sup>41</sup>

A very recent case series<sup>42</sup> confirms the safety and efficacy of adding THC to an existing CBD regime.

In the UK the Twenty 21 observational study sponsored by Drug Science will produce ongoing results, including in epilepsy. (<https://www.drugscience.org.uk/project-twenty-21>). Early results from an audit of 10 patients<sup>43</sup> with severe intractable childhood onset epilepsies demonstrated 97% mean reduction in seizure frequency post-initiation of CBPMs ( $p < 0.01$ ) as well as a reduction in anti-convulsant drug use from a mean of 8 to 1 such medications. All patients were using full-spectrum products with daily dose ranging from 6.6mgs -26.5mgs THC and 200-550mgs CBD. The average cost to these families was £1806.20 per month as they had been forced to use the private market as the NHS consultants would not prescribe. A second audit of a further 10 patients has replicated this and is in press in BMJ Paeds Open.

The MCCS and Drug Science do not propose that these studies are definitive and clearly more studies are needed. However, we do say that these children have reached the end of the road in terms of conventional intervention. There is nothing else that their NHS consultant can suggest.

Thus, given the safety profile, we firmly advise the use of a full-spectrum cannabis medicine supervised by a trained cannabis physician, if the licensed Epidyolex medication has been tried and failed. In other words, full spectrum products should be tried if Epidyolex fails or is associated with unacceptable side-effects.

- 3.6 There is concern about the effect of exposure to THC on the developing brain of both the younger child and adolescent. There is evidence that chronic high exposure to THC during recreational cannabis use can affect brain development, structure and mental health. These effects are seen more clearly in adolescents than in adults<sup>26</sup>.

The evidence for low-dose THC exposure causing any long-term brain development problems is at best minimal and is limited to high THC "street" cannabis. Some studies feel that the long-term cognitive impairment has been overstated<sup>38</sup>. We cannot find evidence of long-term cognitive damage when using low THC medical products for epilepsy. We also point out that taking multiple licensed anti-convulsants can be detrimental and then there is the potential long-term damage caused by multiple seizures.

A physician always needs to balance the risks and benefits in any therapeutic decision and we consider that in children with intractable epilepsy that balance of risks v benefits is firmly in favour of trying the effect of a full-spectrum, anti-convulsant product if the licensed medication

(Epidyolex) has failed to improve the seizures or the child is experiencing unacceptable side-effects.

Finally, we note that in any case Epidyolex contains THC (approx. 3mgs for every 1000mgs CBD). Thus it is somewhat disingenuous of the BPNA to promote the use of Epidyolex but not the use of THC-containing, full-spectrum products.

3.7 THC may also have cardiac effects via its action on CB1 receptors in the myocardium and vascular endothelium. There are a growing number of case reports associating marijuana use with adverse cardiovascular consequences including myocardial infarction, cardiac arrhythmias (atrial fibrillation, atrioventricular block, ventricular tachycardia and asystole), cardiomyopathies and stroke. **We are not aware of any adverse cardiac effects associated with use of CBPMs containing THC in children with epilepsy, (MCCS/DS emphasis)** but cardiac effects should be explored in any clinical trial of these products in children.

3.8 Little is known about the long-term effects of medicinal use of CBD. CBD has been associated with the development of structural brain abnormalities in some animal experiments.

CBD has been used for centuries as a medical product. There is no evidence of any long-term problem with CBD prescription. An extensive report on CBD undertaken in 2018 by the WHO found CBD to be generally well tolerated with low toxicity and a good safety profile.

<https://www.who.int/medicines/access/controlled-substances/CannabidiolCriticalReview.pdf>

3.9 We have found no high quality scientific or clinical evidence in humans to support the suggestion that the addition of THC, in combination with CBD, increases efficacy of CBPMs as anti-epileptic medication in children. **However, there is considerable evidence from Real World data (see section 3.5.1).**

## 4. Background considerations for prescribers

- 4.1 While the 2018 changes made by the Home Secretary moved CBPMs from Schedule 1 to Schedule 2 to allow their legal use, the responsibility for the prescribing and potential adverse effects of a CBPM prescription remains with the prescribing clinician. The evidence base for the efficacy and safety of most of the CBPMs is extremely limited. You should be aware of the GMC guidance on the prescription of unlicensed medications (see 4.6).

If the physician is only interested in “pharmaceutical” data for cannabis, then this is probably true but (as described in more detail above) the efficacy and safety data from other studies is significant and striking.

- 4.2 The Medicines & Healthcare Products Regulatory Agency (MHRA) has a standard of what constitutes a “pharmaceutical grade” product<sup>27</sup>:

Good Manufacturing Practice (GMP) - the minimum standard that a medicine manufacturer must meet in their production processes; and cannabis based medical products (CBPMs) are to GMP standards and indeed this is requirement of importation by the MHRA.

Good Distribution Practice (GDP) – medicines are obtained from the licensed supply chain and are consistently stored, transported and handled under suitable conditions.

This is also true of CBPMs.

- 4.3 Some CBPMs are manufactured to this standard and some are not.

This is incorrect. All imported products (and all products are imported) are to a GMP or equivalent standard.

Such manufacturing and distribution standards do not equate to a formal Licence. The MHRA have published (November 2018) guidance on ‘The supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans ‘specials’<sup>28</sup>. Section 12, regarding pharmacovigilance and reporting of Adverse Drug Reactions (ADR), notes:

“As for all unlicensed medicines manufacturers should report the suspected ADR immediately and in no case later than 15 calendar days from receipt, stating that the product is unlicensed. It is a mandatory requirement to electronically report suspected ADRs. The ICH-E2B international standard electronic report should be used and the report should be electronically submitted via the EudraVigilance European Gateway (see MHRA or European Medicines Agency (EMA) websites for more details).

Prescribers or pharmacists supplying the “special” should report using the electronic Yellow Card (found at <http://www.mhra.gov.uk/yellowcard>), the Yellow Card app or using a paper form stating the manufacturer and indicating that the product is unlicensed. Wholesalers supplying unlicensed CBPMs are under an obligation to keep records of any adverse reaction of which they become aware and report any serious adverse reaction to the MHRA; this should be done by submission of a ‘Yellow Card’ report.

This is correct and CBPMs are subject to the same standard of adverse event reporting as any other medicine. There is not a lower standard for CBPMs

For CBPMs the MHRA requires reporting of ALL suspected adverse reactions (serious and non-serious, whether the product is licensed or unlicensed), including reports of failure of efficacy. Given the limited safety data that is currently available on the products, the MHRA will be conducting enhanced vigilance activities to support their safe use.

These obligations are placed on any person selling or supplying “specials”, not only manufacturers, importers and distributors but also the Specialist doctor prescribing the unlicensed CBPMs where appropriate. An adverse reaction means a response to a medicinal product which is noxious and unintended.”

This again is the same standard as any medicine. The standard of vigilance for CBPMs is no different from any other medicine.

#### 4.4 In summary, CBPMs can be categorised into four types:

- i. Medicines that are authorised in the UK (and other EU members states) (e.g. Sativex for spasticity in Multiple Sclerosis – contains both THC and CBD; Epidyolex® in conjunction with clobazam for treatment resistant epilepsy in Dravet syndrome and Lennox-Gastaut syndrome).
- ii. Medicines that have undergone randomised controlled trials, have an EMA licence in place and have a UK application in progress (currently Epidyolex® – in Tuberos Sclerosis Complex).
- iii. Non-licensed, GMP and GDP standard products (e.g. Bedrocan and Tilray products – varying preparations that have different combinations and proportions of CBD and THC). They have not undergone RCTs and are not in the process of applying for an EMA licence.

Many of the imported CBPMs have been thoroughly studied in observational trails, n-of-1 trials, case studies and through other Real World evidence studies – as outlined above.

- iv. Non-licensed, non-GMP, non-GDP standard products. This category will include all the artisanal cannabis oils. In these products there is limited knowledge of the relative doses of cannabinoids, their consistency from batch to batch, or the presence of contaminants.

This is correct but “artisanal” products are not legal for prescription and thus not being prescribed. No one is suggesting that “street” cannabis should be used.

Medications are licensed in the UK after they have been through a strictly monitored development process. This process involves preliminary lab-based research and testing the medicine in patients in randomised controlled clinical trials. The MHRA will grant a licence for use in a specific clinical indication and in a specific age-group if the medicine has proven efficacious in clinical trials and if strict safety / quality standards are met.

There are many instances of products being issued with a medical license that have not been through double-blind placebo-controlled studies. The paper by Hatswell and colleagues showed

that 76 drugs had been approved in a 15 year period (1999-2014) by the FDA and EMA without RCT evidence<sup>44</sup>.

The implication that this is the only route acceptable for a licensed product is simply incorrect. It is also worth remembering that the vast majority of medicines prescribed for children are prescribed as off-label medicines as clinical trials for licensing are only undertaken in adult populations.

**In paediatric practice doctors prescribe both licensed and unlicensed medications** (MCCS / Drug Science emphasis). In the significant majority of unlicensed paediatric prescribing situations, the unlicensed product is prescribed 'off label'. This means a licensed drug is used outside its original indication or outside its licensed age group. For example, a medication licensed for adults, which is then prescribed for a child.

With the exception of Epidyolex® which is licensed, CBPM products for epilepsy are not licensed for any indication or age group. Therefore, unlike products being prescribed 'off label', there is no regulated trial efficacy or safety data on which to rely.

There is significant volume of efficacy and safety data. Full spectrum cannabis as a plant does not lend itself to randomized double blind placebo-controlled trials. Indeed, for a full spectrum plant such trials are impossible and if physicians are waiting for such evidence it will never materialise (see section 2.1.5)

Outside the confines of a clinical trial setting, you should be aware that this form of prescribing is largely untested in UK clinical practice.

There are now over 10000 patients prescribed CBMPs in the UK including about 150 children with resistant epilepsy.

Over 50 countries globally have permitted the use of cannabis-based medicines on prescription. There are now thousands of children with epilepsy who are being prescribed whole plant medical cannabis products, often demonstrating significant improvements in seizure control and overall quality of life. We are therefore in a somewhat fortunate position in that we can observe and learn from our experienced counterparts from overseas and in we should focus our attention on more established medical cannabis markets where prescribing in paediatric populations is more prevalent.

4.5 The GMC has published guidance on prescribing unlicensed medications<sup>29</sup>. It states (para 106):

“When prescribing an unlicensed medicine you must:

- a. be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy
- b. take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so
- c. make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine.”

- 4.6 Randomised controlled trial data exist only for the use of CBD (Epidyolex®) in three conditions associated with refractory epilepsy (Dravet syndrome, Lennox-Gastaut syndrome and Tuberous Sclerosis Complex).

It is illogical to suggest that Epidyolex is only efficacious in these syndromes. Epidyolex is an anti-convulsant and thus not likely to be specific to these syndromes. Some physicians have been denying children access to this medicine (even Epidyolex) on the grounds that the child does not have Dravet or Lennox-Gastaut or Tuberous Sclerosis. Some of the childhood epilepsy syndromes are so rare that there will never be studies. Are these children to be forever excluded from what could be a life-changing treatment?

## 5. Guidance for clinicians on prescribing cannabis-based products for medicinal use

5.1 The BPNA has carefully considered the issue of who prescribes CBMP's. We defer to the GMC, NHS England and devolved nations and NICE who have clear guidelines on this. These state:

In order to **initiate prescription** of a cannabis-based product for medicinal use, you must be on the Specialist Register. The GMC advise that clinicians should prescribe only within their relevant specialist registration/training. For a child with intractable epilepsy, NICE and NHSE predicate prescription should be made by a Consultant Paediatric Neurologist- see below. NICE Clinical Guideline [CG137] 1.10<sup>30</sup> states that:

"1.10.1 All children, young people and adults with epilepsy should have access via their specialist to a tertiary service when circumstances require."

[Note: for children and young people, the specialist is a paediatrician and the tertiary service is paediatric neurology.]

It is legal and acceptable for a paediatrician with an interest in epilepsy to prescribe. Shared care with a cannabis trained physician is also acceptable as determined by the recent GMC case brought against a paediatric rheumatologist by the BPNA. This case was rejected as the doctor was prescribing safely and attempted to do so on a shared care basis. The BPNA doctors involved failed to respond to requests to share care and the GMC's own expert felt that the BPNA was not acting in the Best Interests of the children. It is only the BPNA who feel that a paediatric neurologist should prescribe. This is ideal, but if none are doing so then, in the presumed view of the BPNA, the child should not receive such medication, despite evidence that the CBPM is helping that child?

In the view of the MCCA and Drug Science this is a totally unacceptable position. The NICE guidance states that:

- *"After the initial prescription, subsequent prescriptions of cannabis-based medicinal products may be issued by another prescriber as part of a shared care agreement under the direction of the initiating specialist prescriber, if:*
- *shared care is appropriate and in the person's best interest*
- *the person's clinical condition is stable*
- *the other prescriber is confident to make a fully informed prescribing decision about cannabis-based medicinal products".*

"1.10.2 If seizures are not controlled and/or there is diagnostic uncertainty or treatment failure, children, young people and adults should be referred to tertiary services soon for further assessment. Referral should be considered when one or more of the following criteria are present:

- the epilepsy is not controlled with medication within 2-years



- management is unsuccessful after two drugs
- the child is aged under 2-years
- a child, young person or adult experiences, or is at risk of, unacceptable side effects from medication
- there is a unilateral structural lesion
- there is psychological and/or psychiatric co-morbidity
- there is diagnostic doubt as to the nature of the seizures and/or seizure syndrome”

The NICE guideline on cannabis-based medicinal products [NG144]<sup>31</sup> states that “the initial prescription of cannabis-based medicinal products (excluding nabilone, THC:CBD spray [Sativex] and medicines not classified as controlled drugs such as cannabidiol) must be made by a specialist medical practitioner (a doctor included in the register of specialist medical practitioners [the Specialist Register], see section 34D of the Medical Act 1983<sup>32</sup>. They should also have a special interest in the condition being treated (see the GMC’s information for doctors on cannabis-based products for medicinal use<sup>33</sup>). For children and young people under the care of paediatric services, the initiating prescriber should also be a tertiary specialist.”

The BPNA have conveniently failed to quote the recent NICE Guidance:

*“The (original) guideline made research recommendations for the use of unlicensed cannabis-based medicinal products for severe treatment-resistant epilepsy. The committee took the view, based on the evidence available at the time, that there was insufficient evidence of safety and effectiveness to support a population-wide practice recommendation (that is, a recommendation relating to the whole population of people with severe treatment-resistant epilepsy).*

*3.2 The fact that NICE made no such population-wide recommendation should not however be interpreted by healthcare professionals as meaning that they are prevented from considering the use of unlicensed cannabis-based medicinal products where that is clinically appropriate in an individual case. Patients in this population can be prescribed cannabis-based medicinal products if the healthcare professional considers that that would be appropriate on a balance of benefit and risk, and in consultation with the patient, and their families and carers or guardian.*

*3.3 There is no recommendation against the use of cannabis-based medicinal products.(our emphasis). For more information about why the committee decided not to recommend against use of these products, see the rationale section of the guideline.*

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Tertiary paediatric specialists with appropriate training to manage drug resistant epilepsies are accredited paediatric neurologists.

As per GMC Good medical practice, “You must recognise and work within the limits of your

competence<sup>34</sup>. We strongly recommend that only specialists with paediatric neurology expertise and training prescribe for children in this context.

The MCCS and Drug Science strongly recommend that paediatricians with an interest can prescribe CBPMs either after training or in a shared care agreement with a cannabis physician, in the event that paediatric neurology colleagues are unwilling to cooperate in the Best Interests of the child.

If a paediatric neurologist does feel it is appropriate to prescribe an unlicensed cannabis-based product for medicinal use, then it is recommended that they ensure the patient also fulfils the criteria that must be met before a licensed CBPM is prescribed within the NHS. Specifically, that they meet as a minimum the following three criteria:

- 5.1.1 Have an epilepsy that has proven intractable to treatment with at least two conventional licensed anti-epileptic drugs given at therapeutic doses
- 5.1.2 Have not responded to the ketogenic diet or for whom the diet is inappropriate.
- 5.1.3 Have been assessed for epilepsy surgery and are considered unsuitable or unlikely to achieve seizure freedom with a procedure.

The MCCS and Drug Science are astonished that the BPNA recommends consideration of epilepsy surgery ahead of a safe and potentially efficacious plant-based medicine.

We feel this is totally unacceptable and unethical practice.

## Cannabidiol

- 5.2 Current level 1 evidence for the use of CBPMs suggests efficacy and short-term safety of CBD (Epidyolex®) in two epileptic encephalopathies (Dravet and Lennox-Gastaut syndromes) and in refractory epilepsy associated with Tuberous Sclerosis Complex. Epidyolex® has been licensed in the UK for the treatment of Dravet and Lennox-Gastaut syndromes when used in conjunction with clobazam. It has been licensed by the EMA for use in refractory epilepsy associated with tuberous sclerosis complex both with and without clobazam and a decision on UK licensing is awaited. There are also open-label studies suggesting efficacy of CBD (Epidyolex®) in other childhood epilepsies.

Given the current level of published evidence, we advise that pure CBD should be used when considering prescription of a CBPM in intractable epilepsy in children.

The MCCS and Drug Science agree that the licensed product Epidyolex be used first in intractable epilepsy. We recognise that Epidyolex does not always produce the desired effect or has unacceptable side effects. In such circumstances then a full-spectrum plant product should be considered as described below.

### Dosing regime for CBD (Epidyolex®):

The trial evidence suggests that dose of 10-20mg/kg/day of CBD (Epidyolex®) is effective at reducing seizures in Dravet and Lennox-Gastaut syndromes. Dosing typically starts between

2-5mg/kg/day and is increased until seizures are reduced or the patient experiences adverse effects that lead to discontinuation. The upward titration rate should not exceed a dose increase of 5mg/kg/day each week. In the trials there was no increased effectiveness obtained by a dose of 20 mg/kg/day as compared with 10 mg/kg/day and there were more side-effects noted at the higher dose.

In the tuberous sclerosis complex RCT, a dose of 25 mg/kg/day was compared with 50 mg/kg/day and with placebo. Both the 25mg/kg/day and 50 mg/kg/day regimes were more efficacious than placebo but there was no difference in efficacy between the low and high dose CBD regimes. Again, there were more side-effects noted with the higher dose.

As with all seizure medications we would advocate using the least dose that is effective. We would not advise going beyond 50 mg/kg/day.

The MCCS and Drug Science notes that Epidyolex also contains “inactive” ingredients, including dehydrated alcohol (7.9% w/v), sesame seed oil, strawberry flavor, and sucralose. These ingredients can cause issues such as allergy and in higher doses the alcohol content could also be a problem for children. We remind prescribers again that Epidyolex contains small amounts of THC.

The MCCS and Drug Science recommend starting, after Epidyolex, with a high CBD, low THC oil CBMP (such as Bedrolite although others are now available – details from the MCCS) at a dose of about 1mg/kg/day. The dose should be slowly escalated at about 5-day intervals to a maintenance dose which is normally around 10mgs/kg/day. The full spectrum products need lower dosing (and thus have fewer side effects generally) than Epidyolex. If the response is still inadequate at that dose a small amount of THC (from a balanced oil or high THC oil) could be added at a dose of about 0.25mgs/kg/day escalating slowly to a dose, if necessary, of up to about 10mgs in total per day.

Existing anti-convulsants (except Epidyolex) should be continued although it is common for pre-existing anti-convulsants to be reduced in either dose or number once a maintenance level of CBMP has been obtained.

- 5.3 Care should be taken when using CBD (Epidyolex®) with other anti-epileptic drugs. It may alter drug levels of benzodiazepines, rufinamide, topiramate, zonisamide and eslicarbazepine. Particular care should be exercised when using with clobazam as it will increase N-desmethylclobazam levels. Raised liver enzyme levels (AST and ALT) are commonly seen when CBD (Epidyolex®) is used in conjunction with sodium valproate.
- 5.4 When using CBD (Epidyolex®) liver function tests should be taken at baseline, 2-weeks post the initiation of therapy and 2-weeks after each increment in dose. They should then be performed at regular intervals or on the occurrence of a clinically relevant event.
- 5.5 CBD (Epidyolex®) has shown efficacy as add-on therapy in addition to the patient’s regular anti-epileptic medication. We recommend using it in this context and not as a substitute for regular treatment.
- 5.6 If CBD (Epidyolex®) shows no evidence of effectiveness in reducing seizure frequency after six

months of treatment then we recommend that it should be withdrawn.

The MCCS and Drug Science point out that it is not uncommon for a child to take some weeks to stabilize on a CBPM. We suggest a three-month trial period for Epidyolex in the dose escalating regime described above. We agree that Epidyolex should be withdrawn slowly in such circumstances and a full-spectrum product slowly substituted as described in section 5.2.

## Other CBPMs (including those containing THC)

5.7 We do not currently make a positive recommendation for prescribing other non-licensed cannabis-based products for medicinal use whether or not they comply with good manufacturing practice (GMP) or good distribution practice (GDP) standards. Products with higher proportions of THC (>0.2%) that meet GMP and GDP standards have no randomised controlled clinical trial evidence of safety or efficacy in children and young adults with epilepsy... although there is considerable Real-World evidence as outlined in section 3.5. The MCCS and Drug Science do not understand the relevance of the 0.2% THC level. If the BPNA is suggesting that this is the legal level allowed for an over-the-counter CBD product then they are wrong. The legal limit is 1mg of controlled cannabinoid per container (bizarrely regardless of the size of the container).

The NICE Guideline committee on the use of cannabis-based medicinal products [NG144] also noted that current research in this area is limited and of low quality and agreed that it did not warrant a practice recommendation<sup>31</sup>.

This statement has been modified by NICE as quoted on page 14.

5.8 NICE issued a clarification to NG144 in March 2021<sup>35</sup>. This clarification reiterated the position of the original NICE guideline committee that there was insufficient evidence of safety and effectiveness to support a practice recommendation for unlicensed CBMPs. The clarification, however, also stated that individual clinicians could prescribe unlicensed CBMPs if they felt it was clinically appropriate. The NICE clarification did not materially change the recommendations given in their original guideline.

The latter sentence is untrue. The clarification of the previous guidance fundamentally changed the previous recommendation.

5.9 Clinicians should not feel under pressure to prescribe unlicensed CBPMs as these products have not undergone appropriate clinical trials and Level 1 evidence has not been established for these drugs.

The clinician in our view needs to weigh the totality of the evidence against the clinical needs of the child, as in any clinical situation.

We recommend that these products undergo randomised clinical trials for efficacy and safety before they are routinely prescribed in the UK. We welcome the re-scheduling of these products from Schedule 1 to Schedule 2 that will enable their investigation in clinical trials, and we further welcome the re-scheduling of pure cannabidiol (Epidyolex is not a pure cannabidiol) from schedule 2 to schedule 5.

As we have stated CBMP full spectrum products cannot go through a pharmaceutical type of randomized study. If such evidence is awaited, they will never be prescribed. A different assessment is required. Cannabis is not a pharmaceutical product. It is a plant-based product and needs assessing as such.

- 5.10 We recognise that it is each individual specialist clinician's decision whether to prescribe an unlicensed medicinal product and we also recognise **that the responsibility for prescribing an unlicensed medicine rests solely with the prescribing clinician.** (our emphasis). However, we do not currently recommend the initiation of unlicensed CBPMs in children with complex epilepsy.

The MCCS and Drug Science fundamentally differ with this narrow-minded approach to the safety and wellness of a child with severe refractory epilepsy.

## Artisanal Cannabis Oils and non-prescribed CBPMs

- 5.11 We do not recommend the prescription of artisanal cannabis oils. Artisanal products are manufactured outside a laboratory that would meet the standards normally required for the manufacture of pharmaceutical products. These products will not meet GMP and GDP standards. They will contain both CBD and THC in varying quantities and proportions. Different batches of the same product may have different concentrations of constituents and the labelling of constituents may be inaccurate.

The MCCS and Drug Science agree that prescription of "artisanal" products is not recommended as such products remain illegal. We presume the BPNA means products grown at home or supplied by an illegal dealer. All products prescribable in the UK are fully approved under a MHRA import license.

- 5.12 We recommend that clinicians ask carers if they are administering to the child any other compounds, particularly non-prescribed CBPMs. In such a case, the clinician should monitor effects on liver function and look for potential drug interactions, particularly with benzodiazepines and sodium valproate.

## Prescribing CBPMs in private practice

- 5.13 If a Paediatric Neurologist does plan to prescribe an unlicensed CBPM in private practice, they should:

5.13.1 inform the NHS Paediatric Neurologist normally looking after the child and

5.13.2 provide ongoing comprehensive care for a child with complex epilepsy, including appropriate psychological, developmental and physical assessment/therapy, with 24-hour support.

If a paediatrician with an interest in epilepsy prescribes a CBMP then, if a tertiary specialist is involved, then that specialist should be informed and should work on a shared care basis with the paediatrician and/or the cannabis physician. It is unacceptable practice for a tertiary paediatric neurologist to refuse to continue to care for a child because they have

been prescribed a legal CBMP. If this happens the MCCS and Drug Science will inform the GMC.

- 5.14 If a paediatric neurologist prescribes an unlicensed CBPM in private practice they should also be certain that the family can sustain the cost of ongoing private prescriptions. The MCCS and Drug Science finds this totally unacceptable. It is not in any way standard practice for a doctor to enquire whether a family can support funding in the long term. Affordability assessments are not within the role or remit of a prescribing clinician and do not apply to any other private medical services in the UK (which currently serve approximately 11% of the population). Such an enquiry is unethical and such a situation would of course not arise if a doctor prescribed on the NHS, as is legal. It can be argued that the stance of the BPNA is driving patients and their families into private practice and in some cases into the black market. That is an unethical situation. We consider it unethical to initiate a treatment in private practice for which funding is not available in the longer term. The NHS is unlikely to meet the cost of future prescriptions of an unlicensed medicine that has no Level 1 evidence of efficacy and safety.

The BPNA should not make such assumptions. That is a matter for Government.

### Patients who are taking unlicensed CBPMs admitted to NHS hospitals

- 5.15 There have been examples of patients who have been admitted to NHS hospitals whilst taking unlicensed CBPMs. These have been either a GMP/GDP product prescribed in private practice, or a legal (containing <0.2% THC) or illegal (containing >0.2% THC – incorrect interpretation of the law) artisanal product that has been accessed independently by the patient's family. We recommend that each NHS Trust formulates a policy on their approach to this situation. If a medicine is legal then prescription should continue in hospital. To do otherwise is totally unacceptable and unethical practice. The implication that any medicine with greater than 0.2% THC is illegal is wrong and a misinterpretation of the law – even the law regarding over-the-counter CBD products. The BPNA should not be making false and misleading statements. The law for over-the-counter (OTC) products is that the container should not contain more than 1mg of controlled cannabinoid. Drug licensing factsheet: cannabis, CBD and other cannabinoids - GOV.UK (www.gov.uk). The OTC CBD products should by definition contain less than that. The MCCS and Drug Science recognise that some patients try an OTC CBD product prior to prescription. We do not recommend such practice as the products are unsupervised and by law the producer cannot make any medical claim and thus the patient is unguided.

### When clinicians are pressurised to prescribe against their clinical judgement

- 5.16 If a doctor feels under pressure to prescribe a medication that they believe is not in the patient's interests, the doctor should follow the GMC guidance "Consent: patients and doctors making decisions together"<sup>36</sup>. Paragraph 49 states:

"If a patient asks for treatment or care that you don't think would be in their clinical interests, you should explore their reasons for requesting it, their understanding of what it would involve, and their expectations about the likely outcome. This discussion will

help you take account of factors that are significant to the patient and assess whether providing the treatment or care could serve the patient's needs. If after discussion you still consider that the treatment or care would not serve the patient's needs, then you should not provide it. But, you should explain your reasons to the patient and explore other options that might be available, including their right to seek a second opinion."

Doctors should only prescribe medications if they are satisfied they serve the patient's needs.

The physician should take into account the BPNA guidance but also other guidance that may be at variance with the BPNA position, as in this critique.

## Guidance for transition to adult care

5.17 If a paediatric neurologist is prescribing a licensed CBPM to a patient that is transitioning to adult care, they should ensure that they have re-assessed the epilepsy syndrome/ diagnosis and the efficacy of the CBMP for that particular patient before they hand over care to adult services, making sure that they continue to meet the NHS criteria for prescription of the licensed CBPM.

*Criteria – Dravet or Lennox-Gastaut syndromes, frequency of the countable seizures reduced by 25% based on seizure diaries collected by patients, parents or carers or frequency of target seizure types have reduced by 30% compared to baseline e.g. drop seizures in LGS.*

They should present the adult neurologist with the baseline seizure burden prior to instituting CBMP therapy, subsequent assessment of seizure burden, as well as other parameters including quality of life, cognition and independence. It is important to note that there needs to be a continued reduction of seizure frequency for the adult neurologist to be able to continue to prescribe CBMP. Where children have been taking the CBMP for longer than two years prior to transition, it is good practice to consider withdrawal of therapy for a trial period to see whether it is still effective and assess that the patient continues to meet the criteria for CBMP. Where a paediatrician initiates CBMP therapy within two years of transition, they should make sure that there is an agreement with the relevant adult neurologists that the prescription can be maintained prior to initiation.

If a paediatric neurologist is prescribing an unlicensed CBPM in private practice, they should ensure there is transition to an adult neurologist in private practice who is willing provide ongoing comprehensive care for an adult with complex epilepsy.

## 6. Research Recommendations

The NICE Guideline committee made specific research recommendations with respect to CBPMs in severe treatment-resistant epilepsies, specifically:

(i) What is the clinical and cost-effectiveness of CBD in epileptic disorders in children, young people and adults?

(ii) Does the addition of THC to CBD have an effect on seizure frequency, brain structure and neuropsychological performance when compared with both CBD alone and placebo in epileptic disorders in children, young people and adults?

We recommend that research RCTs are undertaken in children with refractory epilepsies comparing CBD versus CBD+THC versus Placebo. A three-arm (CBD vs CBD+THC vs Placebo) trial design is preferable to a two-arm (CBD+THC vs Placebo) design given the existing Level 1 evidence that CBD is efficacious in some paediatric epilepsies.

Outcomes should include seizure frequency, neuropsychological performance, cost-effectiveness and quality of life. Adequate safety information should be collected during any trial that includes specific information re neurological and cardiac effects as well as general information re adverse events.

The MCCS and Drug Science again note that RCTs are not possible, desirable or practical for a plant-based product. The BPNA is stuck in a pharmaceutical industry model



## 7. The negative consequences of the BPNA guidance

The BPNA paper (*Guidance on the use of cannabis-based products for medicinal use in children and young people with epilepsy (Oct 2021)*) has failed to recognise the downside of their own recommendations.

There is no recognition of the fact that these children have uncontrolled, drug resistant epilepsy, by definition. They have a poor quality of life, often difficulties in school and in play and at home and the whole family suffers from the consequences. We point out that recurrent seizures are damaging to the developing brain and such severe seizures are associated with a risk of status epilepticus and death. Every avenue must be explored in attempt to alleviate the seizures.

Cannabis is not a cure-all and is not the right medication for every child (or adult). However, it has been shown to have efficacy in many cases and is generally remarkably safe. It should be prescribed by trained cannabis physician. The MCCS is happy to train any paediatrician free of charge and thereafter mentor and guide them through the cannabis prescription process.

All medical practitioners, and in particular the BPNA executive committee, should note the General Medical Council “Good Medical Practice” principles.

We specifically draw attention to these points:

- Make the care of your patient your first concern.
- Treat patients as individuals and respect their dignity.
- Work in partnership with patients.
  - Listen to, and respond to, their concerns and preferences.
  - Give patients the information they want or need in a way they can understand.
  - Respect patients’ right to reach decisions with you about their treatment and care.
  - Support patients in caring for themselves to improve and maintain their health.
- Work with colleagues in the ways that best serve patients’ interests.
- Never discriminate unfairly against patients or colleagues.
- Remember you are personally accountable for your professional practice (*and not the BPNA*)

Professor Helen Cross was the first clinician to prescribe an unlicensed medicine for childhood epilepsy in 2003. That was a brave and correct move when a child was in extremis. It is a pity that the current members of the executive committee have reverted to an old and outdated paradigm of efficacy to the clear detriment of many thousands of children in the UK.

**We call for recognition of the value of cannabis based medicinal products by sensible and caring paediatricians in the UK.**

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**Commentary and critique on the  
BNPA publication:**

Guidance on the use of cannabis-based  
products for medicinal use in children and  
young people with epilepsy (Oct 2021)

By the  
Medical Cannabis Clinicians Society &  
Drug Science



Medical Cannabis  
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