BPNA
British Paediatric Neurology Association

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

31 October 2018

Contents

Glossary

ACMD	Advisory Committee on Misuse of Drugs
ADR	Adverse drug reaction
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BPNA	British Paediatric Neurology Association
CBD	Cannabidiol
CBPM	Cannabis-based product for medicinal use
EMA	European Medicines Agency
GDP	Good distribution practice
GMC	General Medical Council
GMP	Good manufacturing practice
NICE	National Institute of Clinical Excellence
NHS	National Health Service
MHRA	Medicines & Healthcare Products Regulatory Agency
RCT	Randomised controlled trial
THC	Tetrahydrocannabinol

1 Introduction

The British Paediatric Neurology Association (BPNA) has been asked 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 products for medicinal use in children and young people with epilepsy. The BPNA has been asked to highlight the key questions specialist clinicians should address before considering prescribing and also provide guidance on appropriate dosage and treatment regimes.

This interim guidance is a prelude to formal guidance being issued by the National Institute of Clinical Excellence (NICE) in or around October 2019. It has been approved by the Association of British Neurologists and the British Chapter of the International League Against Epilepsy.

2 Background

2.1 The Chief Medical Officer, Professor Dame Sally Davies produced a review of the therapeutic and medicinal benefits of cannabis based products in June 2018[1]. 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 of reviews" 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"[2-9]

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).

2.2 The Advisory Committee on Misuse of Drugs (ACMD) has given advice to the Home Secretary on cannabis-based products for medicinal use (CBPM) and a summary of this advice is that[10]:

2.2.1 Products with a clear definition are moved out of the currently illegal Schedule1 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[11].

2.3 The following definition of a cannabis-based product for medicinal use (CBPM) has been formally agreed by the Government:

2.3.1 It contains cannabis, cannabis resin, cannabinol or a cannabinol 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 UK government proposed prescribing framework:

2.4.1 Prescribing will be restricted to doctors on the Specialist Register, prescribing only within their relevant specialist registration.

2.4.2 There will be three access routes:

- Prescribing these products will treated as “Specials”; in other words, 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

2.4.3 The assumption is that such prescribing is “a last resort” and “used only when no other drug with MHRA marketing authorisation meets the clinical need”.

2.4.4 Responsibility remains with the prescribing clinician.

2.4.5 This government guidance applies to both public and private sectors.

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

3 Summary of current knowledge

3.1 The BPNA has previously produced a public statement on the use of cannabis related products[12]. In particular, there is brief summary of the issues around the two most investigated compounds, cannabidiol (CBD) and tetrahydrocannabinol (THC). There is good quality clinical evidence that CBD has an anti-epileptic effect in two severe epilepsy syndromes (Dravet Syndrome and Lennox-Gastaut Syndrome) and evidence from open-label studies and animal studies that it is likely to have an anti-epileptic effect in the epilepsies in general[13-19]. It has multiple molecular targets and does not interact with cannabinoid receptors in the hippocampus. THC may also have an anti-epileptic effect, although some animal studies suggest that it can also have a pro-convulsant effects[12]. 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.

3.2 There have been open-label and uncontrolled studies of cannabidiol (CBD) showing seizure reduction in epilepsy[14,17,18,20]. Since 2017, three double blind, randomised controlled trials of pure CBD (Epidiolex ®) in Dravet's syndrome and Lennox Gastaut syndrome have been published[13,15,19]. The median monthly reduction in seizure frequency was significantly greater in patients randomised to CBD compared to patients on placebo. Similarly, there was a greater than 50% reduction in convulsive or drop seizures in significantly more patients randomised to CBD compared to those patients on placebo. Sedation, diarrhoea and loss of appetite were common adverse effects.

3.3 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 and eslicarbazepine. 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[21].

3.4 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[16]. 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[22]. However, the study was small, unblinded and had no control group and therefore does not constitute high quality evidence of either effectiveness or safety.

3.5 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[23].

3.6 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.

4 Background considerations for prescribers

4.1 While the changes put forward by the Home Secretary are moving 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 will remain 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. You should also investigate whether your medical protection insurance and hospital indemnity will cover you for the prescription of unlicensed CBPMs.

4.2 The MHRA has a standard of what constitutes a "pharmaceutical grade" product[24]:

> Good Manufacturing Practice (GMP) - the minimum standard that a medicine manufacturer must meet in their production processes; and
>
> Good Distribution Practice (GDP) - medicines are obtained from the licensed supply chain and are consistently stored, transported and handled under suitable conditions.

4.3 Some CBPMs are manufactured to this standard and some not. Such manufacturing and distribution standards do not equate to a formal Licence. The MHRA are publishing (November 2018) guidance on 'The supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans 'specials''[25]. 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 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.
>
> 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."

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 MS – contains both THC and CBD).

ii. Medicines that have undergone randomised controlled trials and have an EMA application in progress (currently Epidiolex® – pure CBD product).

iii. Non-licensed, GMP and GDP standard products (e.g. possibly Bedrocan and Tilray products – varying preparations that have different combinations and proportions of CBD and THC) that have not undergone RCTs and are not in the process of applying for an EMA licence.

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.

4.5 Licensed medications are formally approved by the MHRA for use in a specific clinical indication and in a specific age-group. In paediatric practice doctors prescribe both licensed and unlicensed medications. In the significant majority of paediatric prescribing situations this unlicensed category is "off label", i.e. the use of a licensed drug used outside its original indication or outside its licensed age group (e.g. a medication licensed for adults, which is then prescribed by a paediatrician for a child). It is important to be aware that most potential CBPM prescribing will not fall within either of these categories.

Most potential CBPM prescribing will not fall within the traditional off-label use of a licensed medicine seen widely in paediatric practice. Outside the confines of a clinical trial setting, you should be aware that this form of prescribing is largely untested in UK clinical practice.

4.6 The GMC has published guidance on prescribing unlicensed medications[26]. It states:

"When prescribing an unlicensed medicine you must:

- be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy
- 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

- 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.

4.7 Randomised controlled trial data exist only for the use of CBD (Epidiolex®) in two epilepsy syndromes (Dravet syndrome and Lennox-Gastaut syndrome). Anecdotal and other weaker evidence suggests there may be a benefit in expanding Epidiolex® prescribing to other intractable epilepsies in children and young people.

5 Guidance for clinicians on prescribing cannabis-based products for medicinal (CBPMs)

5.1 In order to prescribe a cannabis-based product for medicinal use, you must be on the Specialist Register. It is further advised that clinicians should prescribe only within their relevant specialist registration. Consequently, for a child with intractable epilepsy, the prescription should be made by a Consultant Paediatric Neurologist. NICE Clinical Guideline [CG137] 1.10[27] 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.]
>
> "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
> - The 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"

As per GMC guidance "*Good medical practice* says that you recognise and work within the limits of your competence"[28] and expertise. We strongly recommend that only specialists with paediatric neurology expertise and training prescribe for children in this context.

5.2 Prescription of a non-licensed cannabis-based product for medicinal use should be used as a treatment of last resort for children who meet the following three criteria:

5.2.1 Have an epilepsy that has proven intractable to treatment with conventional licensed anti-epileptic drugs given at therapeutic doses.

5.2.2 Have not responded to the ketogenic diet or for whom the diet is inappropriate.

5.2.3 Are not candidates for epilepsy surgery.

5.3 Current best evidence for the use of CBPMs suggests efficacy and short-term safety of CBD (Epidiolex®) in two epileptic encephalopathies (Dravet and Lennox-Gastaut syndromes). There are also open-label studies suggesting efficacy in other childhood epilepsies. We advise that pure CBD (Epidiolex®) should be the default choice when considering prescription of a CBPM in intractable epilepsy in children. It does not yet have an EMA licence and is currently going through the application process. It has already acquired a licence from the US Food and Drug Administration.

Dosing regime for CBD (Epidiolex®):

The trial evidence suggests that dose of 20mg/kg/day of CBD (Epidiolex®) 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/week. Doses up to 50mg/kg/day have been used in some open-label studies.

5.4 Care should be taken when using CBD (Epidiolex®) 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 (Epidiolex®) is used in conjunction with sodium valproate.

5.5 When using CBD (Epidiolex®) 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.

5.6 CBD (Epidiolex®) 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.

5.7 If CBD (Epidiolex®) shows no evidence of effectiveness in reducing seizure frequency after four months of treatment then we recommend that it should be withdrawn.

5.8 We do not recommend 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 people with epilepsy. Clinicians should not feel under pressure to prescribe CBPMs until they have undergone appropriate clinical trials. 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.

5.9 We do not recommend the prescription of artisanal cannabis oils. 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.

5.10 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.

5.11 We recommend that patients who are already taking other cannabis-based products of GMP and GDP standard that contain higher proportions of THC (>0.2%) with apparent benefit are transitioned to CBD (Epidiolex®) until robust evidence emerges of these products safety and efficacy.

5.12 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"[29]. Paragraph 5d states:

> "If the patient asks for a treatment that the doctor considers would not be of overall benefit to them, the doctor should discuss the issues with the patient and explore the reasons for their request. If, after discussion, the doctor still considers that the treatment would not be of overall benefit to the patient, they do not have to provide the treatment. But they should explain their reasons to the patient, and explain any other options that are available, including the option to seek a second opinion."

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

6 References

1. Davies PDS. Cannabis Scheduling Review Part 1: The therapeutic and medicinal benefits of Cannabis based products - a review of recent evidence. London: Department of Health and Social Care. 2018 https://www.gov.uk/government/publications/cannabis-scheduling-review-part-1

2. The National Academies of Sciences Engineering and Medicine. The Current State of Evidence and Recommendations for Research Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. 2017

3. Health Products Regulatory Authority (Ireland). Cannabis for Medical Use – A Scientific Review. 2017

4. World Health Organisation Expert Committee on Drug Dependence. Cannabidiol (CBD) Critical Review Report. 2018

5. World Health Organisation Expert Committee on Drug Dependence. Cannabidiol (CBD) Expert Peer Review 1. 2018

6. World Health Organisation Expert Committee on Drug Dependence. Cannabidiol (CBD) Expert Peer Review 2. 2018

7. World Health Organisation Expert Committee on Drug Dependence. Pre-review: Cannabis plant and resin. 2018

8. World Health Organisation Expert Committee on Drug Dependence. Pre-review: Extracts and tinctures of cannabis. 2018

9. Australian Government Department of Health Therapeutic Goods Administration. Medicinal cannabis - guidance documents. 2018

10. Advisory Council on the Misuse of Drugs. Scheduling of cannabis-derived medicinal products: Advisory Committee on Misuse of Drugs response. 2018

11. Rt Hon Sajid Javid MP. Scheduling of cannabis-derived medicinal products: response to Advisory Committee on Misuse of Drugs. 2018

12. British Paediatric Neurology Association. BPNA statement on use of marijuana (cannabis) related products in the treatment of complex epilepsies. 2018

13. Devinsky O, Cross JH, Laux L, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. The New England Journal of Medicine 2017;**376**(21):2011-20 doi: 10.1056/NEJMoa1611618[published Online First: Epub Date]|.

14. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. The Lancet. Neurology 2016;**15**(3):270-8 doi: 10.1016/S1474-4422(15)00379-8[published Online First: Epub Date]|.

15. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;**391**(10125):1085-96 doi: 10.1016/S0140-6736(18)30136-3[published Online First: Epub Date]|.

16. Rosenberg EC, Patra PH, Whalley BJ. Therapeutic effects of cannabinoids in animal models of seizures, epilepsy, epileptogenesis, and epilepsy-related neuroprotection. Epilepsy & Behavior : E&B 2017;**70**(Pt B):319-27 doi: 10.1016/j.yebeh.2016.11.006[published Online First: Epub Date]|.

17. Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex(R)) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Epilepsy & Behavior : E&B 2018;**86**:131-37 doi: 10.1016/j.yebeh.2018.05.013[published Online First: Epub Date]|.

18. Chen KA, Farrar M, Cardamone M, et al. Cannabidiol for treating drug-resistant epilepsy in children: the New South Wales experience. The Medical journal of Australia 2018;**209**(5):217-21

19. Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. The New England Journal of Medicine 2018;**378**(20):1888-97 doi: 10.1056/NEJMoa1714631[published Online First: Epub Date]|

20. Stockings E, Zagic D, Campbell G, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. J Neurol Neurosurg Psychiatry 2018;89(7):741-753 doi: 10.1136/jnnp-2017-317168

21. Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. Epilepsy & Behavior : E&B 2017;**70**(Pt B):313-18 doi: 10.1016/j.yebeh.2016.11.016[published Online First: Epub Date]|.

22. McCoy B, Wang L, Zak M, et al. A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome. Annals of clinical and translational neurology 2018;**5**(9):1077-88 doi: 10.1002/acn3.621[published Online First: Epub Date]|.

23. Lubman DI, Cheetham A, Yucel M. Cannabis and adolescent brain development. Pharmacology & Therapeutics 2015;**148**:1-16 doi: 10.1016/j.pharmthera.2014.11.009[published Online First: Epub Date]|.

24. Medicines and Healthcare Products Regulatory Agency & Department of Health and Social Care. Good manufacturing practice and good distribution practice. 2014 (updated 2018)

25. Medicines and Healthcare Products Regulatory Agency. The supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use in humans 'specials'. November 2018

26. General Medical Council. Prescribing unlicensed medicines. 2018

27. NICE Clinical Guideline [CG137] Epilepsies: diagnosis and management. Updated 2018. https://www.nice.org.uk/guidance/cg137/chapter/1-Guidance#referral-for-complex-or-refractory-epilepsy

28. General Medical Council. Good practice in prescribing and managing medicines and devices. 6. Keeping up to date and prescribing safely. 25 February 2013. https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/keeping-up-to-date-and-prescribing-safely

29. General Medical Council. Consent: patients and doctors making decisions together. 2 June 2008. Page 8. https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent