

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

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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
IMP	Investigational medicinal product
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) 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].

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 2018¹. 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”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) gave advice to the Home Secretary on cannabis-based products for medicinal use (CBPM) and a summary of this advice is that¹⁰:

- 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 2018¹¹.

- 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.
 - 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”.
 - 2.5.4 Responsibility remains with the prescribing clinician.
 - 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.

3 Summary of current knowledge

- 3.1 The BPNA has previously produced a public statement on the use of cannabis related products¹². 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 general¹³⁻¹⁹. 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 effects¹². 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^{14,17,18,21}. 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^{13,15,19,20}. 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.
- 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-desmethyclobazam, 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 time²².
- 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 THC¹⁶. 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 effectiveness²³. 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

nonrandomised 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 frequency²⁴. 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 visits²⁵. Again, the studies are vulnerable to bias due to their uncontrolled designs.

- 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 adults²⁶.
- 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, 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.
- 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.

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).

4.2 The Medicines & Healthcare Products Regulatory Agency (MHRA) has a standard of what constitutes a “pharmaceutical grade” product²⁷:

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 are not. 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’²⁸. 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.

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 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 Tuberous 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.
- 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.

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.

In paediatric practice doctors prescribe both licensed and unlicensed medications. 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.

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

4.5 The GMC has published guidance on prescribing unlicensed medications²⁹. 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).

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 prescribe 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] 1.10³⁰ 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
- 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]³¹ 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 1983³². 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 use³³). For children and young people under the care of paediatric services, the initiating prescriber should also be a tertiary specialist.”

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”³⁴. We strongly recommend that only specialists with paediatric neurology expertise and training prescribe for children in this context.

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

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.

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.

- 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-desmethyclobazam 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.

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.

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 recommendation³¹.

- 5.8 NICE issued a clarification to NG144 in March 2021³⁵. 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.
- 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.

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 from schedule 2 to schedule 5.

- 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. However, we do not currently recommend the initiation of unlicensed CBPMs in children with complex 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.
- 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.
- 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. 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.

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) 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.

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"³⁶. 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.

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.

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