

# Ending the pain of children with severe epilepsy? An audit of the impact of medical cannabis in 10 patients

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## Abstract

**Background:** Scientific and anecdotal evidence suggest that whole plant cannabis extracts are effective in reducing seizure frequency in individuals with a range of epileptic etiologies. We report a case series of 10 individuals using CBMPs in the UK to treat their conditions.

**Methods:** In this retrospective study, we report on patients (aged 2–48) with severe, intractable, childhood onset epilepsies using combined cannabinoid therapy. Carers of patients provided details through the charity ‘End our Pain’ and these data were subsequently analysed. Our primary objective was to assess changes in monthly seizure frequency pre and post initiation of CBMPs. We also report on previous and current AED, CBD:THC daily dose, quality of life and financial costs associated with CBMP private prescription. Change in monthly seizure frequency were assessed using a Wilcoxon Signed-ranks test.

**Results:** Of the 10 patients enrolled in the study there was an 97% mean reduction in monthly seizure frequency post initiation of CBMPs which was statistically significant ( $Z = 0$ ,  $p < 0.01$ ). We showed a reduction in AED use following initiation of CBMPs from a mean of 8 ( $\pm 5.98$ ) to 1 ( $\pm 1.05$ ). All patients were using either Bedrolite or Bedica (Bedrocan International) as their CBMP. Individual daily doses of THC ranged from 6.6mg – 26.5mg and for CBD, 200 mg – 550 mg. Average monthly cost of CBMP was £1816.20.

**Interpretation:** Our findings suggest a combination of CBD and THC based products are effective in reducing seizure frequency in a range of epileptic conditions. We highlight the inefficacy of the healthcare system in supporting these patients who bare great personal and financial burdens. We encourage specialist physicians and relevant bodies to permit greater ease of access of these medications to those patients where efficacy has been shown.

## Keywords

CBD, CBMPs, epilepsy, medical cannabis, pediatric, THC

## Introduction

Cannabis has a long history in medicine, having been used for millennia until being banned in the UK under the 1971 Misuse of Drugs Act (Nutt, 2019). today’s use of ‘medical cannabis’ has had a short past. It was restored to the UK pharmacopeia in November 2018 following a landmark case involving Alfie Dingley, a boy who had his epilepsy successfully treated in the Netherlands with medical cannabis and whose condition severely deteriorated when prevented from accessing these medications. A number of other parents of children with similarly severe and intractable epilepsy also sought treatment overseas with notable significant success but at a huge personal financial cost: several like Alfie’s mother having to live abroad to obtain treatment. About twenty of these families formed a

charity called ‘End our Pain’ to call for medical cannabis to be made legal in the UK and so allow them to access this treatment at home.

Under UK law cannabis is considered a Class B controlled drug under Part II, Schedule 2, of the Misuse of Drugs Act 1971. It is also additionally listed under Schedule 1 of the Misuse of Drugs Regulations (MDR) 2001. Cannabis includes both the

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primary psychoactive component,  $\Delta^9$ -tetrahydrocannabinol (THC) and the non-psychoactive cannabidiol (CBD). THC is controlled under the Misuse of Drugs Laws however, CBD is not listed as a controlled substance in the UK. The therapeutic application of cannabis. It medication often contains a mix of both the psychoactive and non-psychoactive elements of cannabis and has therefore proven difficult to provide a legislative framework for its use within the medical field in the UK with current laws.

Following the Alfie Dingley campaign in November 2018, the UK government amended the MDR 2001 to place 'cannabis-based medicinal products' (CBMP) into schedule 2 which allowed for them to be prescribed in the UK by specialists without a Home Office license (Health and Social Care Committee, 2019). Although medical cannabis was made available in November 2018 under the Medicines and Healthcare Regulatory Agency (MHRA) Specials Licence, since then there have been only 20 NHS prescriptions made available (Conservative Drug Policy Reform Group, 2020). At present, the National Institute for Clinical and Healthcare Excellence (NICE) recommends the prescription of the CBMP; cannabidiol, for two rare, severe forms of epilepsy: Lennox-Gastaut syndrome (LGS) and Dravet syndrome as an adjunct to clobazam (National Institute for Health and Care Excellence, 2019). The justification for other children with epilepsy being refused NHS prescriptions is usually that there is insufficient of medical cannabis efficacy in their conditions, a statement which is in complete contrast to many children's personal medical experience.

As a result of these strict recommendations, many patients who could potentially benefit from medical cannabis are not benefitting from the changes in law. A recent survey estimates that 1.4 million individuals in the UK are using medical cannabis without a prescription, for a broad range of indications, often sourced from the black market with all the risks this entails. It was also estimated in the same survey that 11.8% of epilepsy sufferers are using a CBMP therapeutically (Centre for Medical Cannabis, 2020).

CBMPs refer to a range of different whole plant products (usually in the form of oily extracts that are taken sublingually) that usually contain varying doses of CBD or THC plus the hundreds of other cannabinoids, terpenes and other molecules found in the cannabis plant (Atakan, 2012). THC, responsible for the 'stoning' effect has been found to have anti-convulsant (Devinsky et al., 2014), analgesic and anti-spasticity properties which are thought to be related to its interaction with the CB1 receptor (CB1R) (Häuser et al., 2018; Flachenecker, 2013). CBD is thought to exert its anti-convulsant effects independent of the CB1R (Pertwee,

2008). Potential mechanisms include antagonism of the lipid activated GPR55 - expressed on both inhibitory and excitatory synapses modulating synaptic excitability and plasticity (Lanuti et al., 2015; Sylantsev et al., 2013). Other proposed mechanisms include; agonism of TRP cation channels (De Petrocellis et al., 2012), the 5HT1-a receptor (Fogaça et al., 2014) and indirect modulation of the endocannabinoid system through blocking anandamide uptake and hydrolysis leading to an increase in CB1R activation (Sylantsev et al., 2013).

A recent systematic review of 35 studies and 4 RCTs investigating cannabis based medication for paediatric epilepsies found all studies to date used CBMPs as adjunctive treatment with the majority using cannabidiol alone (Elliott et al., 2020). Total monthly seizures were found to have been reduced by CBD compared to placebo with a median reduction of 19.8% in the RCTs and by 30-90% in the non-randomised study, with these effects being maintained through at least 48 weeks of treatment in some children (Elliott et al., 2020). In spite of these promising results there remains a paucity of evidence in products containing both CBD and THC.

There is evidence to suggest there is benefit from the therapeutic combination of these respective cannabinoids. A recent study assessing the use of 100 mg/ml CBD and 2 mg/ml THC in 20 patients with Dravet's syndrome reported a median reduction of 70.6% ( $p < 0.05$ ) in motor seizures, reductions in electroencephalograph (EEG) activity and significant improvements in quality of life (Warren et al., 2017). Further, a multi-centre study from Israel found 89% of participants seeing a reduction in seizure frequency following administration of medication with a 20:1 CBD:THC dosing regimen (Tzadok et al., 2016). Another study employing the same dosing regimen in 46 patients with various epilepsy etiologies found 56% of patients to have a  $\leq 50\%$  reduction in mean monthly seizure frequency (Hausman-Kedem et al., 2018).

Whilst these studies report a clear benefit of combined CBD:THC medications they are limited in being restricted to one disorder in the former study and having fixed dosing regimens in the two latter Israeli studies. In current clinical practice dosing generally begins with low THC and higher CBD doses, with THC added if breakthrough seizures develop. Therefore, in our study we did not limit inclusion to the study based on diagnosis and all participants were on individualised dosing regimens to better reflect the clinical picture at the population level.

It is essential to document these cases so that patients who have benefitted from medical cannabis can continue to do so and so that the empirical evidence for CBMP efficacy in epilepsy can be broadened. We have collated data from the parents of 10 children

on the impact of CBMPs in these families. of seizure frequency, adverse effects and quality of life in the children before and after the Records initiation of CBMPs were provided and of which we report these findings here.

## Methods

### Study design and participants

We conducted a retrospective study based on records provided by carers of participants being treated with CBMPs for their epilepsy to the End our Pain' database.

Carers of participants were asked to provide charity's the following information, details of which can be found in Table 1; patient's age, diagnoses, current AED (please state name/s), previous AED (please state name/s), previous CBMP, number of seizures pre-CBMP, number of seizures post-CBMP, Cost of CBMP. We also calculated the daily dose of THC and CBD that participants received from their CBMP.

The cohort included participants who are treated with a private prescription of a CBMP in the United Kingdom who have a diagnosis of epilepsy.

Statistical analysis was performed comparing pre and post CBMP data. The non-parametric Wilcoxon Signed-Rank Test was employed to test for significant differences between seizure frequency pre and post initiation of CBMP with significance set to 0.05 using Microsoft excel 2016.

### Study medication

In all the cases reported in our audit the cannabis products used were either Bedrolite (containing <1% THC and 9% CBD), or Bedica (containing 14% THC and <1% CBD) both produced by Bedrocan International.

The study was approved by the Imperial College Research Ethics Committee (20IC5830 ICREC Committee 01/05/2020).

## Results

The following table reports on the previously outlined variables in 10 participants using CBMPs to treat epilepsy (Table 1).

A total of 10 participants from the End our Pain database were included. Our main findings indicate a range of ages (2–48 years) and different, previously intractable epileptic conditions for which CBMPs have proven to be effective in reducing seizure frequency. Five patients had an undiagnosed epilepsy, three patients had a diagnosis of LGS, one had CFC syndrome and one had Doose syndrome. We also report

on individuals previous and current AEDs, which show a decrease in the average number of AEDs post initiation of CBMP from 8 ( $\pm 5.98$ ) to 1 ( $\pm 1.05$ ). One patient had previously been on a ketogenic diet and 2 patients were currently using VNS to also manage their seizures. All of the participants were using either Bedrolite or Bedica (Bedrocan International) as their CBMP. Individual daily dose of THC ranged from 6.6 mg – 26.5 mg and for CBD, 200 mg – 550 mg. We also collected data on monthly cost of CBMP prescriptions for participants and report an average spend of £1816.20 per participant.

Figure 1 shows the findings of the individual and average change in seizure frequency pre and post initiation of CBMP. Monthly seizure frequency in individuals ranged from 37.5–18,000 pre-initiation of CBMP and between 0 – 750 post-initiation of CBMP. A Wilcoxon Signed-Ranks Test indicated that within the cohort the monthly seizure frequency post CBMP initiation was statistically significantly lower than monthly seizure frequency prior to CBMP initiation  $Z=0$ ,  $p < 0.01$ .

Additionally, carers reported reductions in panic attacks, insomnia, increases in cognitive ability and function as well as improvements in behaviour, emotional regulation and speech following initiation of CBMPs. No adverse side effects of CBMPs were reported by carers.

## Discussion

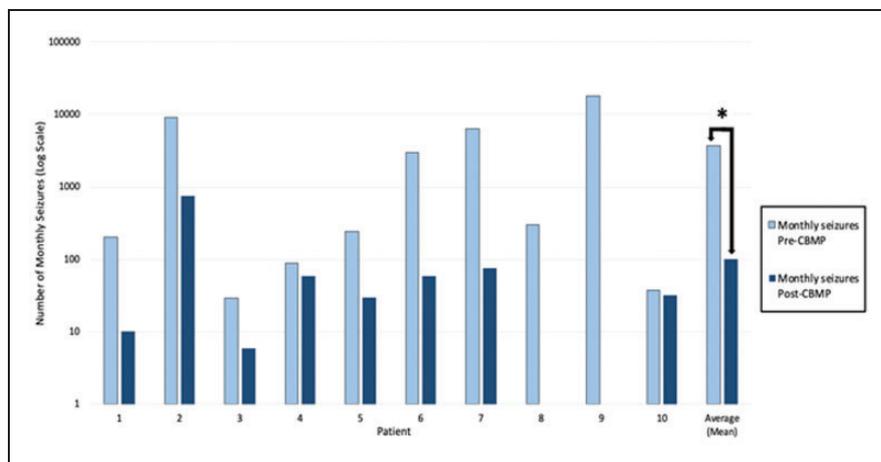
This case series highlights the motivation for the parent group to make medical cannabis available in the UK. Patients presented with a range of epileptic etiologies and each had a significant reduction in monthly seizure frequency. Participants had a range of AEDs prior to initiation of CBMP with little benefit and sometimes significant cognitive and motor impairments. As well as this we highlighted the financial costs of CBMPs. One patient was allowed to leave institutional care for the first time in a decade.

In line with previous studies reporting reduction in seizure frequency using a combination of CBD and THC we found an average reduction in monthly seizures of 97% which was statistically significant ( $p < 0.01$ ) (Hausman-Kedem et al., 2018; Tzadok et al., 2016; Warren et al., 2017). Our findings reflect the clear benefit of combined cannabinoid pharmacological therapy in resolving epileptic activity in a range of disorders. A recent meta analysis by Elliot and colleagues found that cannabidiol alone was no different to placebo in 4 RCT's in gaining seizure freedom and improving quality of life in treating paediatric epilepsies (Elliott et al., 2020). In our study four patients had failed on cannabidiol alone (Epidiolex), the NICE

**Table 1.** Participant characteristics.

Patient	Age	Diagnosis	Previous AED/treatment	Current AED/ treatment	Previous CBMP medication	Current CBMP medication	Daily dose of CBMP medication (ml)	Daily dose of THC (mg)	Daily dose of CBD (mgs)	Monthly seizures pre CBMP	Monthly seizures post CBMP	Monthly CBMP cost
1	26	LGS	Clobazam, Lamotrigine	VNS	None	Bedrolite + Bedica	3.9 ml Bedrolite, 0.39 ml Bedica	19.8	390	200	10	£2,000.00
2	10	LGS	Clobazam, Clonazepam, Ethosuximide, Lacosamide, Lamotrigine, Levetiracetam, Phenobarbital, Phenytoin, Prednisolone, Rufinimide, Sodium valproate, Topiramate	Lamotrigine	Epidiolex	Bedrolite	3.25 ml	9.75	325	9000	750	£2,500.00
3	16	Pharmaco-resistant epilepsy, Cluster Focal Seizures	Carbamazepine, Clobazam, Lacosamide, Lamotrigine, Levetiracetam, Phenytoin, Sodium valproate	Phenytoin	None	Bedrolite + Bedica	5.5 ml Bedrolite, 0.5 ml Bedica	26.5	550	29	6	£2,620.00
4	2	CFC Syndrome	Levetiracetam	Clobazam, Phenobarbital	None	Bedrolite + Bedica	2 ml Bedrolite, 0.08 ml Bedica	4.6	200	90	60	£1,197.00
5	4.5	Intractable epilepsy due to in utero seizure caused by genetic mutation	Clobazam, Prednisolone, Pyridoxine, Levetiracetam, Vigabatrin	Ketogenic Diet	Epidiolex, Haleighs hope	Bedrolite	3 ml	9	300	240	30	£1,000.00
6	18	LGS	20+ AEDs and Ketogenic diet	VNS	Charlottes web hemp, Endoca	Bedrolite + Bedica	3.8 ml Bedrolite, 0.15 ml Bedica	14.4	380	3,000	60	£2,100.00
7	10	Uncontrolled Epilepsy & Autism, possible PVL, focal epilepsy and every seizure type, Autism, Right sided cerebral palsy	Chloral hydrate, Clobazam, Clonazepam, Diazepam, Ethosuximide, Lamotrigine, Levetiracetam, Phenobarbital, Phenytoin, Sodium valproate, Steroids, Topiramate, Zonisamide	Clobazepam, Levetiracetam, Phenobarbital	Epidiolex	Bedrolite + Bedica	3.6 ml Bedrolite, 0.45 ml Bedica	19.8	360	6300	75	£2,115.00
8	2	Undiagnosed, potentially rare mitochondrial disorder from NARS2 gene mutation	Carbamazepine, Clobazam, Levetiracetam, Phenobarbital, Sodium valproate, Steroids, Topiramate, Vigabatrin	Clobazam	Epidiolex	Bedrolite	2.2 ml	6.6	220	300	0	£1,280.00
9	7	Doose Syndrome	Sodium valproate	Lamotrigine, Zonisamide	None	Bedrolite and Bedica	3.1 ml Bedrolite, 0.2 ml Bedica	13.3	310	18000	0	£1,350.00
10	48	Refractory focal Epilepsy and Autism	10+ AEDs	None	Bedica, Endoca	Bedrolite	3.5 ml	10.5	350	37.5	32.4	£2,000.00

LGS: Lennox-Gastaut syndrome; VNS: vagal nerve stimulation; AED's: anti-epileptic drugs; CFC: Cardiofaciocutaneous; NARS2: N Asparaginyl-TRNA Synthetase 2; CBMP: Cannabis based medicinal product.



**Figure 1.** Log scale of monthly seizure frequency pre & post initiation of Cannabis Based Medicinal Products. \* $P < 0.01$ .

recommended CBMP for epilepsy, suggesting a mixture of compounds inclusive of THC was a key component in achieving clinical success.

The recent report from the Centre for Medical Cannabis estimated that upto 1.4 million people in the UK are currently self-medicating with cannabis, including upto 12% of the epileptic population (Centre for Medical Cannabis, 2020). With an estimated 600,000 epilepsy sufferers in the UK that is an estimated 72,000 individuals who are currently using a CBMP in the UK, of which only 20 have been prescribed by the NHS since November 2018 (Conservative Drug Policy Reform Group, 2020; Joint Epilepsy Council of the UK and Ireland, 2011). Our study provides a small case series of some of the most severe of these patients with a range of childhood-onset epilepsy diagnoses to give a clinical picture of CBMP effects in this population. The impact of CBMPs in these patients was remarkable and often life-changing.

We accept this is not a randomised and controlled clinical study, but rather a series of  $n = 1$  trials. These of course form the bedrock of medical prescribing since every treatment in every patient is in effect such a trial (Nutt et al., 2020). Ten of these provide powerful evidence of clinical value particularly as all the patients had failed a range of other proven treatments. Given that it would be extremely difficult to conduct randomised studies in this range of different epilepsies with these very ill patients it seems unlikely that any such RCTs could or would be done. In the meantime, we believe this case series provides adequate evidence for neurologists and paediatricians to explore such prescribing in patients with similar epilepsies.

We also draw to attention the high personal financial burden of obtaining private prescriptions of CBMPs. According to the recent survey by the

Centre for Medical Cannabis (Centre for Medical Cannabis, 2020), it was found that average yearly black market purchased medical cannabis equated to £3732.00 contrasted with an average annual cost of £21,794.40 for the private prescriptions for participants within our study.

Additionally, given the current Covid-19 crises we anticipate many participants will struggle to receive their CBMPs whether that be through the NHS, through private prescriptions or through the black market. We envisage that the health of these individuals will be severely compromised and as a result we publish this timely series to encourage clinicians and public health bodies to prioritise the health of these individuals and help them to access the medications they need to survive.

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### Author Contributions

RRZ and DJN analysed the data and developed the initial manuscript. AKS contributed sections on medical cannabis and its background and regulation. All authors reviewed and agreed to the final manuscript.

### Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AKS is Head of Research for the charity Drug Science, which receives an unrestricted educational

grant from a consortium of medical cannabis companies. DJN and RRZ declare no competing interests.

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