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Medical cannabis for severe treatment resistant epilepsy in children – A case series of ten patients

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Abstract

Objectives
Here we report the findings of a case series of ten children suffering with intractable epilepsies in the UK to determine the feasibility for using whole-plant cannabis medicines to treat seizures in children.

Setting
This study was conducted retrospectively through collecting clinical data from carers and clinicians on study outcome variables. Participants were recruited through the MedCann Support and End our Pain charity groups which are patient representative groups that support children who are using medical cannabis to treat their epilepsies. Medicines were administered to patients by clinicians in both NHS and private medical practices. Follow up calls were conducted throughout the period January 2021 to May 2021 to keep data recorded up to date.

Participants
Ten children, 18 years old or less, with intractable epilepsies were recruited from two charities. There were no limitations on diagnosis, sex or ethnic origin.

Interventions
Participants were treated with a range of whole-plant medical cannabis oils. Individual dosing regimens were determined by clinicians.

Primary outcome measure
The primary objective was to assess the impact of this treatment on seizure frequency.

Results
Seizure frequency across all ten participants reduced by 86% with no significant adverse events. Participants reduced use of AEDs from seven to one following treatment. We also note significant financial costs to obtain these medicines through private prescriptions.

Conclusions
This study establishes the feasibility of whole-plant medical cannabis as an effective and well-tolerated medicine for reducing seizure frequency in children suffering with intractable epilepsies. We encourage specialist physicians to prescribe for such patients within the NHS and for regulatory bodies to adapt their recommendations and permit greater access for these medicines.

Key words
Epilepsy, Neurology, Paediatric neurology, Clinical Pharmacology, Medical Cannabis, Cannabis based medicinal products (CBMPs)

Key Messages

What is known about the subject?

- Since the 1800s there has been significant anecdotal evidence of the value of medicinal cannabis in treating childhood epilepsies
- There have been 4 successful RCTs showing the therapeutic efficacy of cannabidiol (CBD) for the treatment of Lennox-Gastaut, Dravet's and Tuberous sclerosis syndrome
- There is little available scientific evidence available that has investigated whole-plant cannabis medicines containing THC in paediatric epilepsies.

What this study adds?

- The reduction of seizures in all 10 children demonstrates feasibility for this form of treatment in patients with paediatric intractable epilepsies
- These findings justify the potential value of further research into the reported therapeutic benefit of whole-plant medicinal cannabis products

Introduction

Though used for millennia in eastern medicine, the advent of medical cannabis as a therapeutic tool to treat seizures in the west was first noted in 1843 by an Irish physician, Dr O'Shaughnessy. He observed that cannabis tinctures resolved seizures in a febrile infant, thus claiming that medicine had found an anticonvulsant of the highest order[1]. In 1971 both recreational and medial cannabis were made illegal under the Misuse of Drugs Act 1971 and so cannabis research largely ceased. Led by parents whose children had responded well to whole-plant medical cannabis extracts but who had failed on conventional anti-epileptic drugs (AEDs) and purified cannabidiol (Epidiolex), medical cannabis was re-initiated as a medicine in the British pharmacopeia in 2018.

Despite the change in legal status of medical cannabis, most of these children have not benefited as to date there has been only 3 NHS Cannabis based medicinal product (CBMPs) prescriptions made in total and only 2 to children[2]. Many patients are thus forced to resort to private treatment which costs up to £2000 per month[3].

Reasons for this resistance are multifactorial[4,5]. One of the most argued by clinicians who might be prescribers is the lack of evidence for efficacy of medical cannabis. By this they usually mean that there are no randomised controlled trials (RCTs) that prove efficacy and without these they are not prepared to prescribe. To a lesser extent this has also limited National Institute for Clinical and Healthcare Excellence (NICE) support[6]. It is generally accepted that the RCTs though powerful are not the only means to generate evidence for the value of treatments. The previous head of NICE and the Medicines Healthcare Regulatory Agency (MHRA) Sir Michael Rawlins in his 2008 Royal College of Physicians Harveian lecture argued that there are many other ways of collecting useful clinical evidence highlighting:

'Randomised controlled trials, long regarded at the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of 'hierarchies' of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base'[7].

In a recent position statement, NICE declared their willingness to acknowledge additional data sources including 'real world' data and 'relevant data collected outside of the context of traditional trials'[8]. One of these other sources of data, real world evidence (RWE) comes from patient case series with before and after outcome measures. These are particularly useful for conditions where RCTs are unlikely or impossible to perform in examples of rare and undiagnosable conditions and especially in paediatric medicine. For this reason, we have conducted an outcome assessment of the use of medical cannabis in 10 children with severe treatment-resistant epilepsy who have all failed on multiple traditional anti-epileptic drugs (AEDs) and many of whom have failed on the licensed cannabidiol (CBD) preparation Epidyolex. Epidyolex is a licensed, pharmaceutical grade, purified CBD medicinal product that is produced by GW Pharma. It is the first and only approved prescription CBD. It is approved to treat seizures associated with Lennox-Gastaut sundrome (LGS), Dravet syndrome or tuberous sclerosis complex (TSC) in patients 1 year of age and over.

Our previous study, a real-world open label retrospective study of the impact of medical cannabis in ten patients found whole plant extracts to be superior to CBD isolate and a mean 80% reduction in seizure frequency in a range of intractable childhood epilepsies where standard treatment had failed[3].

Methods

Study design

We recruited participants through two charities, MedCann Support and End Our Pain, which represent children who are using medical cannabis to treat their intractable epilepsies. At the time of the study there were a total of 40 participants across both charities that were using whole-plant medical cannabis products to treat their epilepsies. The study team liaised with these charities to disseminate the research proposal and participant information sheets to potential participants via the charities email database and social media pages. A total of 26 participants subsequently provided consent for involvement in the study and provided data on study outcome measures. Ten of these are reported in Zafar et al. 2020. Of the remaining 16 participants, only ten participants are involved in this current study. The attrition of six participants were due to missing data (n=5) and being over the age of 18 (n=1). Participant's data were collected from their parents or carers via telephone or video conference calls for the period January 2021 to May 2021.

Patient and Public involvement

Participants, parents, and clinicians helped to design the variables and information collected in the study. Working closely with patient groups will ensure the results are disseminated to relevant stakeholders, including patient representative groups and clinical governance bodies.

Participants

We engaged carers of patients, following their consent to engage in the study, to provide information on patients age, diagnoses, current AED's, previous AEDs, previous CBMPs, current CBMPs, monthly seizure frequency pre and post initiation of CBMPs, dose of THC and CBD and cost of CBMPs. Data were confirmed with clinician reports where available.

Study medication

All participants received whole plant extract CBMPs either through private prescription or through the NHS. The CBMPs used included Bedrolite (<1% THC and 9% CBD), Bedica (14% THC and <1% CBD), Celixir 20 (<1% THC and 20% CBD), Sweet pink CBD (<1% THC and 10.6% CBD), Althea 100 (<1% CBD and 10% CBD). The prescription of these medicines was initiated by clinicians and all participants continued to use these medicines at the last follow up call. Individual dosing regimens are described in Table 1.

Statistical analysis

Descriptive analysis on group percentage change in seizure outcome are provided. Other variables including mean AED use pre and post initiation of CBMP and mean cost are also described. Appropriate Spearman's correlational analysis was used to analyse the relationship between the ratio of prescribed THC: CBD to changes in seizure frequency. No significance testing was performed due to the lack of randomisation[9].

Ethics approval

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

Results

Clinical and demographic details

A total of 10 patients were included in the current study. The mean age of participants was 6.2 years old (range 1-13). All clinical and demographic details can be viewed in the table.

Table 1: Demographic and clinical data from 10 patients enrolled in the study

Patient	Age	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	% Reduction in monthly seizure frequency	Monthly CBMP Cost
1	6	Epidiloex, Bedrolite, Bedica, Bedrocan, THC-A, Charlottes web	Sweet Pink CBD	2 ml	3.8	200	28	5	82	£1600
2	3	Charlottes Web / Hayleighs Hope / Bedrolite and Bedica	Celixir20	2.2ml	6	225	2,800	560	80	£500
3	7	Epidiolex	Bedrolite	1.4ml	4.2	140	600	0	100	£995.97
4	5	ND	Sweet Pink CBD	1.8ml	5.4	180	120	45	62.5	£200
5	4	ND	Bedrolite	1.2ml	3.6	120	2250	225	90	£1300
6	9	Charlottes webb, Hayleighs hope, over the counter CBD	Bedrolite + Bedrocan	3.6ml Bedrolite	14	360	600	10	98	0
7	13	Bedrolite	Celixir20 and Althea100	0.9 ml Celixir20, 0.2ml Althea100	2.9	110	305	42	86	£1389
8	9	Bedrolite and Bedica	Celixir20	0.75ml	2	75	45	5	89	£400
9	5	ND	Bedrolite	1.4ml	4.2	140	800	100	87.5	£730
10	1	Haleighs Hope	Bedrolite + Bedica	1.68ml Bedrolite, 0.1ml Bedica	5.4	168	130	15	88	£750

Epileptic Aetiologies
The patients presented with a range of epileptic aetiologies including predefined syndromes, rare genetic disorders and undiagnosed epileptic encephalopathies. Two patients presented genetic aetiologies (PCDH19 mutation, chromosome deletion), one with Dravets syndrome, one with Doose syndrome, two with CDKL5 deficiency disorder, one with West syndrome, one with Rett Syndrome, one with Aicardi syndrome and one with undiagnosed refractory epilepsy.

Comorbid diagnosis
Three of the participants presented with multiple comorbid diagnoses. The most reported being Infantile spasms (N=2), learning disabilities (N=1) and global developmental day (N=1)

Medication
Patients reported a mean of 7 (± 4.58) anti-epileptic drugs prior to initiation of CBMPs which reduced to a mean of 1 (± 1.23) per patient with 7 patients managing to completely wean off all AEDs. The most common secondary intervention in the cohort was a ketogenic diet (N=4) prior to initiation of CBMP which was not effective in any patient and was subsequently discontinued. One patient had a current vagal nerve stimulation implant.

Two patients using Epidyolex had failed to respond to this NICE recommended CBMP for treatment resistant epilepsy.

One patient saw a significant worsening of symptoms including an increase in seizure frequency when switching from Bedrolite and Bedica products to other whole-plant CBMPs. The other three patients that changed CBMPs from Bedrolite and Bedica to other products noted burden of cost as the primary reason for switching product, though all these patients reported the efficacy of Bedrolite and Bedica in reducing seizure frequency.

Seizure frequency
Figure 1 shows the findings from the ten participants enrolled in this case-series. Here we show individual and mean changes in seizure frequency pre and post initiation of CBMP (Note log 10 scale).

The monthly seizure frequency reduced for all 10 patients with an overall mean of 86%.

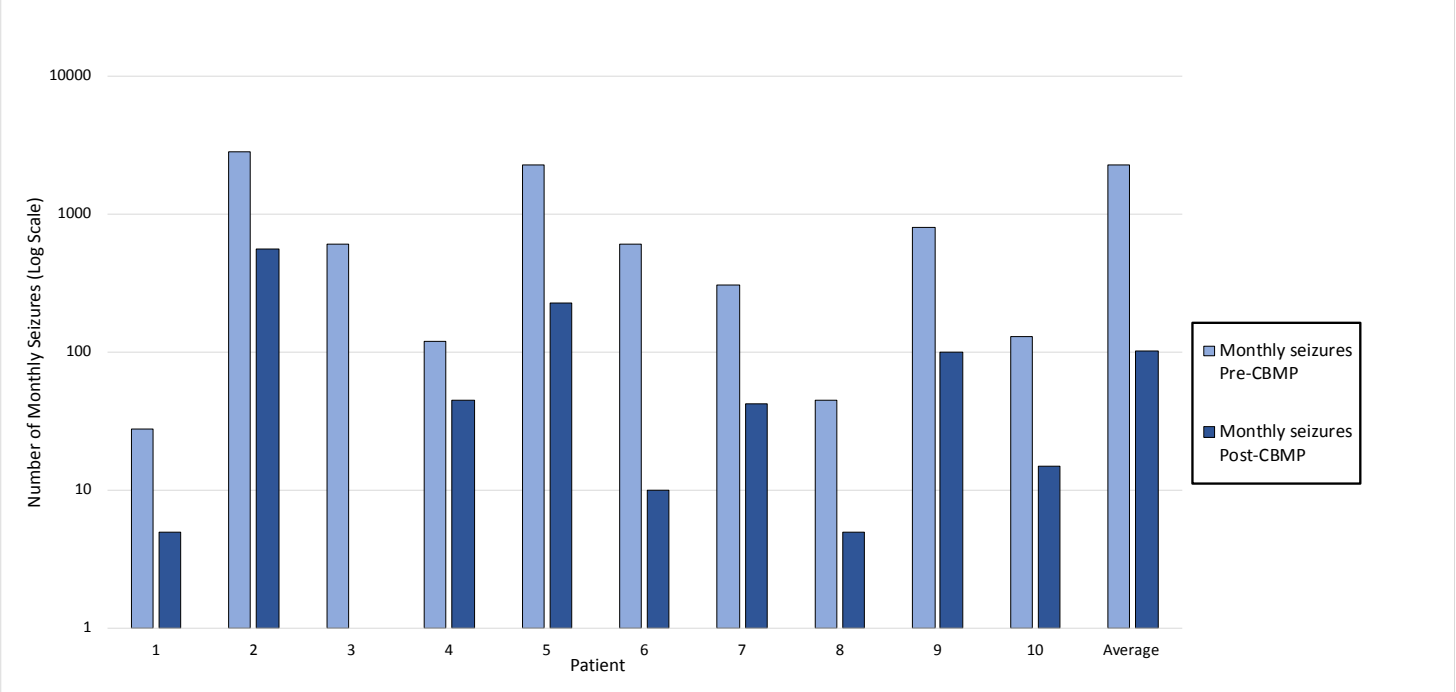

Figure 1. Monthly seizure frequency pre and post CBMP in ten patients suffering with childhood-onset severe intractable epilepsies

Dose of CBMP

All patients were using whole-plant cannabis products which contain a range of terpenes, flavonoids and minor phytocannabinoids. We are currently in process of analysing the respective components of each medication in this study which we plan to report on. For this study we are only able to report on the respective doses of THC and CBD. For THC dosage, patients consumed a mean (SD) of 5.15(± 6.8) mg of THC a day and for CBD 171.8 (± 153.3) mg of CBD daily.

Correlational analysis of CBMP

We correlated the THC: CBD dose ratio against the percent reduction in monthly seizure frequency to see if there were any effects of dosage on reported outcomes. Spearman's rho revealed a non-significant relationship between THC:CBD ratio and changes in seizure frequency (rs =0.271, 9 = 0.292). However, a non-significant trend in the data indicated higher THC dose to be associated with greater reductions in seizure frequency.

Cost

The mean cost for participants medical cannabis prescription was £874 per month. One participant had obtained their medical cannabis prescription for free on the NHS.

Other symptoms

Parents and carers reported significant improvements in health and wellbeing of their children following initiation of whole-plant CBMPs. Particularly, these improvements were noted in sleep, eating, behaviour and cognition. A subset of eleven of these patients across this study and our previous one[3] qualitatively analysed these improvements which are reported in Schlag et al, 2021 (in press). We did not specifically ask for adverse effects, we

asked parents to note if there were any adverse effects in these interviews, but none were reported.

Discussion

This study shows the effectiveness of whole-plant medical cannabis in a group of patients suffering with severe intractable childhood-onset epilepsies. The finding of a mean reduction of 86% in monthly seizure frequency in our (N=10) group demonstrates the feasibility for this medication in such patients. There were no adverse effects reported in response to medical cannabis treatment, and carers reported sustained and significant improvements in behavioural, psychological and cognitive faculties associated with medical cannabis use.

Our findings are in line with several observational and controlled interventional studies that have seen significant reductions in seizure frequency following treatment with medical cannabis. Nonetheless, our data, unlike others in the field, suggest that whole-plant medical cannabis products are superior to isolated CBD products in the patients we examined. To date, double-blind placebo controlled RCT evidence is only available for isolate CBD in three rare forms of epilepsy; Lennox Gastaut syndrome (LG), Dravet syndromes and Tuberous Sclerosis complex [10, 11, 12, 13]. One such study showed a reduction of 22.8% in seizures in children with Dravet syndrome[10] while another study by the same author in LG patients using CBD isolate reported a 42% reduction in drop seizures[11]. To expand on this Thiele et al (2018)[12] conducted a similar double-blind placebo controlled RCT in patients with LG and similarly reported a 44% decrease in drop seizure frequency in the CBD isolate group. A more recent interim analysis of a study by Thiele et al (2019)[13] sought to examine the effects of add-on CBD isolate to standardised treatment for seizures associated with Tuberous Sclerosis Complex, finding a 48% reduction in seizures versus 27% for placebo. From the RCT evidence alone it is clear that CBD isolate is a safe but not especially effective intervention for seizures in LG, Dravet and Tuberous Sclerosis Complex.

As noted by Rawlings[7] there are several limitations of RCTs in assessing evidence for novel medical interventions. For example, the strict inclusion and exclusion criteria of such studies limits the generalisability of findings. This is of particular importance in the case of paediatric-onset intractable epilepsies where the majority of epilepsies diagnosed under the age of 15 are of idiopathic origin[14]. Thus, observational retrospective studies such as ours allow for a wider participation and a broader patient pool to aid in understanding the scope of medical cannabis as an intervention.

Further, placebo-controlled designs fail to show clinicians the value of the intervention relative to standard AEDs or previous care. Moreover, observational studies allow physicians to understand the prescribing history of patients and reflect the effects of clinical decisions rather than RCT driven research interventions with stringent, mildly clinically translatable and often biasedly selected primary endpoints[15].

There are also significant risk and ethical implications associated with randomising children suffering with epilepsy to placebo arms and delaying their treatment. One meta-analysis of placebo controlled randomised trials with AEDs reported a 7-fold increase in risk of sudden unexpected death in epilepsy (SUDEP) in those randomised to a placebo arm[16].

Current NICE guidance, limiting prescribing for medical cannabis for this patient group to cannabidiol in the form of Epidyolex, has relied on just a few RCTs in a limited range of diagnoses. Both of the children in our sample had failed on Epidyolex. For this reason, NICE

guidance has recently been updated to clarify that this should not deter clinicians from prescribing off-license medical cannabis products such as the whole-plant cannabis medicines of which our data give clear support for such prescribing.

Further research is required to elucidate the mechanisms by which the respective additive constituents of whole-plant products lead to superior clinical results. Several encouraging pre-clinical lines of work highlight the anti-convulsive and neuroprotective roles of several minor phytocannabinoids including CBDV, D9-THCV and CBG[17]. THC exerts its anticonvulsant effects via activation of the CB1 receptor and subsequent modulation of glutamatergic excitatory activity in the brain[18]. Nonetheless, the investigation of the putative anti-convulsant effects of these cannabinoids needs to be investigated in-vivo to gain a full appreciation for their therapeutic efficacy.

Mitigating risk is the cornerstone of clinical judgement and there are some opponents of the therapeutic use of THC in children and adolescence. Concern over the deleterious effects of whole-plant medical cannabis must be compared with the known iatrogenic effects of mainline AEDs. One randomised clinical trial of phenobarbital when used chronically for seizure prophylaxis found significant impairment of developmental trajectories[19] as well as a large decrease in global IQ and verbal learning[20]. In another double blind RCT valproate was seen to be associated with poorer attentional performance compared with other AEDs[21].

Additionally, adverse effects from AEDs are the leading cause of treatment discontinuation and after seizure frequency, the major determinant of impaired health-related quality of life in people suffering with epilepsy. Our patient group almost universally reported highly improved cognitive and behavioural outcomes, likely due both to reduced seizure frequency and reduced use of other AEDs.

Finally, we should make it clear that in other medical indications, data obtained other than from RCTs can and does get used by medical regulators. A recent systematic review found that between 1999 and 2014 over 76 unique marketing authorisations were granted without RCT results[22]. Very recently one such drug, Zolgensma[23] for the severe paediatric condition Spinal Muscular Atrophy gained approval on a single-arm open label design with 15 patients.

We believe that our data on whole-plant medical cannabis in childhood-onset severe treatment-resistant epilepsy, provides evidence to encourage its introduction into the NHS within current NICE prescribing guidelines. Such a move would be hugely beneficial to the families, who in addition to having the psychological distress of looking after their chronically ill children, have also to cover the crippling financial burden of their medication.

Data Sharing statement

All the Individual participant data will be available after de-identification and is presented in the table of the manuscript for access by researchers or interested parties.

Author's contributions

RRZ, DJN and LDP analysed the data. All authors developed the initial manuscript and all authors reviewed and agreed to the final manuscript

Conflicts of Interest

AKS is Head of Research for the charity Drug Science, which receives an unrestricted educational grant from a consortium of medical cannabis companies. RRZ, LDP and DJN declare no competing interests.

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Abstract

Objectives
To report the findings of a case series of ten children suffering with intractable epilepsies in the UK to determine the feasibility for using whole-plant cannabis medicines to treat seizures in children.

Setting
This study was conducted retrospectively through collecting clinical data from caretakers and clinicians on study outcome variables. Participants were recruited through the MedCann Support and End our Pain charity groups which are patient representative groups that support children who are using medical cannabis to treat their epilepsies. Medicines were prescribed to patients by clinicians in both NHS and private medical practices. Follow up calls were conducted throughout the period January 2021 to May 2021 to keep data recorded up to date.

Participants
Ten children, 18 years old or under, with intractable epilepsies were recruited from two charities. There were no limitations on diagnosis, sex or ethnic origin.

Interventions
Participants were treated with a range of whole-plant medical cannabis oils. Individual dosing regimens were determined by clinicians.

Primary outcome measure
The primary outcome measure was seizure frequency

Results
Seizure frequency across all ten participants reduced by 86% with no significant adverse events. Participants reduced use of anti-epileptic drugs from an average of seven to one following treatment with medical cannabis. We also noted significant financial costs of £874 per month to obtain these medicines through private prescriptions.

Conclusions
This study establishes the feasibility of whole-plant medical cannabis as an effective and well-tolerated medicine for reducing seizure frequency in children suffering with intractable epilepsies. These findings justify the potential value of further research into the reported therapeutic benefit of whole-plant medicinal cannabis products

Key words
Epilepsy, Neurology, Paediatric neurology, Clinical Pharmacology, Medical Cannabis, Cannabis based medicinal products (CBMPs)

Key Messages

What is known about the subject?

- Since the 1800s there has been significant anecdotal evidence of the value of medicinal cannabis in treating childhood epilepsies
- There have been 4 successful RCTs showing the therapeutic efficacy of cannabidiol (CBD) for the treatment of Lennox-Gastaut, Dravet's and Tuberous sclerosis syndrome
- There is limited scientific evidence available that has investigated whole-plant cannabis medicines containing THC in paediatric epilepsies.

What does this study add?

- The reduction of seizures in all 10 children demonstrates feasibility for this form of treatment in patients with paediatric intractable epilepsies
- These findings justify the potential value of further research into the reported therapeutic benefit of whole-plant medicinal cannabis products

Introduction

Though used for millennia in eastern medicine, the advent of medical cannabis as a therapeutic tool to treat seizures in the west was first noted in 1843 by an Irish physician, Dr O'Shaughnessy. He observed that cannabis tinctures resolved seizures in a febrile infant, thus claiming that medicine had found an anticonvulsant of the highest order[1]. In 1971 both recreational and medial cannabis were made illegal in the UK under the Misuse of Drugs Act 1971 and so cannabis research largely ceased. Led by parents whose children had responded well to whole-plant medical cannabis extracts but who had failed on conventional anti-epileptic drugs (AEDs) and purified cannabidiol (Epidiolex), medical cannabis was re-initiated as a medicine in the British pharmacopeia in 2018.

Cannabis-based medical products (CBMPs) comprise a broad range of medicines. They can be plant-based or synthetic and vary from purified single compounds (often THC or CBD) to complex mixtures of hundreds of molecules, in multiple formulations (oils, solutions, sublingual sprays, tablets and capsules), with multiple delivery mechanisms (oral, nasal, rectal, and inhalation)[2].

Of the products licensed in the UK, Epidyolex (licensed for the treatment of epilepsy) is an isolate, Sativex (recommended for spasticity associated with Multiple Sclerosis) comprises a 1:1 CBD:THC isolate ratio, and Nabilone (e.g., used to treat nausea and vomiting due to cancer chemotherapy) is a THC analogue.

Zafar et al (2020) previously noted that a combination of both THC and CBD from whole plant extracts were necessary for reducing seizure frequency and superior to CBD alone in children suffering from various forms of epilepsy[3].

Despite the change in legal status of medical cannabis, most of these children have not benefited as to date there has been only 3 NHS CBMPs prescriptions made in total and only 2 in children[4]. Many patients are thus forced to resort to private treatment which costs up to £2000 per month[3].

Reasons for this resistance are multifactorial[5,6]. One of the most argued by clinicians who might be prescribers is the lack of evidence for efficacy of medical cannabis. By this they usually mean that there are no randomised controlled trials (RCTs) that prove efficacy and without these they are not prepared to prescribe. To a lesser extent this has also limited National Institute for Clinical and Healthcare Excellence (NICE) support[7]. It is generally accepted that RCTs though powerful are not the only means to generate evidence for the value of treatments. The previous head of NICE and the Medicines Healthcare Regulatory Agency (MHRA) Sir Michael Rawlins in his 2008 Royal College of Physicians Harveian lecture argued that there are many other ways of collecting useful clinical evidence highlighting:

'Randomised controlled trials, long regarded at the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of 'hierarchies' of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base'[8].

In a recent position statement, NICE declared their willingness to acknowledge additional data sources including 'real world' data and 'relevant data collected outside of the context of traditional trials'[9]. One of these other sources of data, real world evidence (RWE) comes from patient case series with before and after outcome measures. These are particularly useful for conditions where RCTs are unlikely or impossible to perform in examples of rare and idiopathic conditions and especially in paediatric medicine. For this reason, we have conducted an outcome assessment of the use of medical cannabis in 10 children with severe treatment-resistant epilepsy who have all failed on multiple traditional anti-epileptic drugs (AEDs) and many of whom have failed on the licensed cannabidiol (CBD) preparation Epidyolex. Epidyolex is a licensed, pharmaceutical grade, purified CBD medicinal product that is produced by GW Pharma. It is the first and only approved prescription CBD. It is approved to treat seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome or tuberous sclerosis complex (TSC) in patients 1 year of age and over.

Our previous study, a real-world open label retrospective study of the impact of medical cannabis in ten patients found whole plant extracts to be superior to CBD isolate and a mean 80% reduction in seizure frequency in a range of intractable childhood epilepsies where standard treatment had failed[3]. A subsequent qualitative follow-up study highlighted the various benefits patients and their families experienced as a result of treatment with CBMPs[2].

Methods

Study design

We recruited participants through two charities, MedCann Support and End Our Pain, which represent children who are using medical cannabis to treat their intractable epilepsies. At the time of the study there were a total of 40 participants across both charities that were using whole-plant medical cannabis products to treat their epilepsies. The study team liaised with these charities to disseminate the research proposal and participant information sheets to potential participants via the charities email database and social media pages. A total of 26 participants subsequently provided consent for involvement in the study and provided data on study outcome measures. Ten of these are reported in Zafar et al. 2020[3]. Of the remaining 16 participants, only ten participants are involved in this current study. The attrition of six

participants were due to missing data (n=5) and being over the age of 18 (n=1). Participants' data were collected from their parents or carers via telephone or video conference calls for the period January 2021 to May 2021.

Study outcomes
The primary study outcome was to assess the percentage change in monthly seizure frequency in participants following initiation of medical cannabis. The secondary study outcomes were to assess the impact of medical cannabis on changes in AED use, to report the concentrations and doses of medical cannabis used by these patients and to document the costs incurred from attaining these prescriptions.

Patient and Public involvement
Participants, parents, and clinicians helped to design the variables and information collected in the study. Working closely with patient groups will ensure the results are disseminated to relevant stakeholders, including patient representative groups and clinical governance bodies.

Participants
We engaged carers of patients, following their consent to engage in the study, to provide information on patients age, diagnoses, current AED's, previous AEDs, previous CBMPs, current CBMPs, monthly seizure frequency pre and post initiation of CBMPs, dose of THC and CBD and cost of CBMPs. Data were confirmed with clinician reports where available.

Study medication
All participants received whole plant extract CBMPs either through private prescription or through the NHS. The CBMPs used included Bedrolite (<1% THC and 9% CBD), Bedica (14% THC and <1% CBD), Celixir 20 (<1% THC and 20% CBD), Sweet pink CBD (<1% THC and 10.6% CBD), Althea 100 (<1% THC and 10% CBD). The prescription of these medicines was initiated by clinicians and all participants continued to use these medicines at the last follow up call. Individual dosing regimens are described in Table 1.

Statistical analysis
Descriptive analysis on group percentage change in seizure outcome are provided. Other variables including mean AED use pre and post initiation of CBMP and mean cost are also described. Appropriate Spearman's correlational analysis was used to analyse the relationship between the ratio of prescribed THC: CBD to changes in seizure frequency. No significance testing was performed due to the lack of randomisation[10].

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

Results

Clinical and demographic details
A total of 10 patients were included in the current study. The mean age of participants was 6.2 years old (range 1-13). All clinical and demographic details can be viewed in table 1.

Table 1: Demographic and clinical data from 10 patients enrolled in the study

Patient	Age	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	% Reduction in monthly seizure frequency	Monthly CBMP Cost
1	6	Epidiloex, Bedrolite, Bedica, Bedrocan, THC-A, Charlottes web	Sweet Pink CBD	2 ml	3.8	200	28	5	82	£1600
2	3	Charlottes Web / Hayleighs Hope / Bedrolite and Bedica	Celixir20	2.2ml	6	225	2,800	560	80	£500
3	7	Epidiolex	Bedrolite	1.4ml	4.2	140	600	0	100	£995.97
4	5	ND	Sweet Pink CBD	1.8ml	5.4	180	120	45	62.5	£200
5	4	ND	Bedrolite	1.2ml	3.6	120	2250	225	90	£1300
6	9	Charlottes webb, Hayleighs hope, over the counter CBD	Bedrolite + Bedrocan	3.6ml Bedrolite	14	360	600	10	98	0
7	13	Bedrolite	Celixir20 and Althea100	0.9 ml Celixir20, 0.2ml Althea100	2.9	110	305	42	86	£1389
8	9	Bedrolite and Bedica	Celixir20	0.75ml	2	75	45	5	89	£400
9	5	ND	Bedrolite	1.4ml	4.2	140	800	100	87.5	£730
10	1	Haleighs Hope	Bedrolite + Bedica	1.68ml Bedrolite, 0.1ml Bedica	5.4	168	130	15	88	£750

Epileptic Aetiologies

The patients presented with a range of epileptic aetiologies including predefined syndromes, rare genetic disorders and undiagnosed epileptic encephalopathies. Two patients presented genetic aetiologies (PCDH19 mutation, chromosome deletion), one with Dravets syndrome, one with Doose syndrome, two with CDKL5 deficiency disorder, one with West syndrome, one with Rett Syndrome, one with Aicardi syndrome and one with undiagnosed refractory epilepsy.

Comorbid diagnosis

Three of the participants presented with multiple comorbid diagnoses. The most reported being Infantile spasms (N=2), learning disabilities (N=1) and global developmental day (N=1)

Medication

Patients reported a mean of 7 (± 4.58) anti-epileptic drugs prior to initiation of CBMPs which reduced to a mean of 1 (± 1.23) per patient with 7 patients managing to completely wean off all AEDs. The most common secondary intervention in the cohort was a ketogenic diet (N=4) prior to initiation of CBMP which was not effective in any patient and was subsequently discontinued. One patient had a current vagal nerve stimulation implant.

Two patients using Epidyolex had failed to respond to this NICE recommended CBMP for treatment resistant epilepsy.

One patient saw a significant worsening of symptoms including an increase in seizure frequency when switching from Bedrolite and Bedica products to other whole-plant CBMPs. The other three patients that changed CBMPs from Bedrolite and Bedica to other products noted burden of cost as the primary reason for switching product, though all these patients reported the efficacy of Bedrolite and Bedica in reducing seizure frequency.

Seizure frequency

Figure 1 shows the findings from the ten participants enrolled in this case-series. Here we show individual and mean changes in seizure frequency pre and post initiation of CBMP (Note log 10 scale).

The monthly seizure frequency reduced for all 10 patients with an overall mean of 86%.

Insert FIG 1

Figure 1. Monthly seizure frequency pre and post CBMP in ten patients suffering with childhood-onset severe intractable epilepsies

Dose of CBMP

All patients were using whole-plant cannabis products which contain a range of terpenes, flavonoids and minor phytocannabinoids. We are currently in process of analysing the respective components of each medication in this study which we plan to report on. For this study we are only able to report on the respective doses of THC and CBD. For THC dosage, patients consumed a mean (SD) of 5.15($\pm$ 6.8) mg of THC a day and for CBD 171.8 ($\pm$ 153.3) mg of CBD daily.

Correlational analysis of CBMP

We correlated the THC: CBD dose ratio against the percent reduction in monthly seizure frequency to see if there were any effects of dosage on reported outcomes. Spearman's rho revealed a moderate correlation between THC:CBD ratio and changes in seizure frequency (r_s =0.271). The trend in the data indicated higher THC dose to be associated with greater reductions in seizure frequency.

Cost

The mean cost for participants medical cannabis prescription was £874 per month. One participant had obtained their medical cannabis prescription on the NHS.

Other symptoms

Parents and carers reported significant improvements in health and wellbeing of their children following initiation of whole-plant CBMPs. Particularly, these improvements were noted in sleep, eating, behaviour and cognition. We did not specifically ask for adverse effects here, but in Schlag et al's (2021) follow up qualitative study (comprising a subset of eleven of these patients across the current study and our previous one [2,3]) parents were asked about adverse effects specifically. Only few minor adverse effects, such as tiredness before exact dosing were reported. Our patient group almost universally reported highly improved cognitive and behavioural outcomes, likely due both to reduced seizure frequency and reduced use of other AEDs.

Discussion

This study shows the effectiveness of whole-plant medical cannabis in a group of patients suffering with severe intractable childhood-onset epilepsies. The finding of a mean reduction of 86% in monthly seizure frequency in our (N=10) group demonstrates the feasibility for this medication in such patients.

Carers reported sustained and significant improvements in behavioural, psychological and cognitive faculties associated with medical cannabis use.

Our findings are in line with several observational and controlled interventional studies that have seen significant reductions in seizure frequency following treatment with medical cannabis. Moreover, our data suggest that whole-plant medical cannabis products are superior to isolated CBD products in the patients examined. To date, double-blind placebo controlled RCT evidence is only available for isolate CBD in three rare forms of epilepsy: Lennox Gastaut syndrome (LG), Dravet syndromes and Tuberous Sclerosis complex [11, 12, 13, 14]. One such study showed a reduction of 22.8% in seizures in children with Dravet syndrome[11] while another study by the same author in LG patients using CBD isolate reported a 42% reduction in drop seizures[12]. To expand on this Thiele et al (2018)[13] conducted a similar double-blind placebo controlled RCT in patients with LG and similarly reported a 44% decrease in drop seizure frequency in the CBD isolate group. A more recent interim analysis of a study by Thiele et al (2019)[14] sought to examine the effects of add-on CBD isolate to standardised treatment for seizures associated with Tuberous Sclerosis Complex, finding a 48% reduction in seizures versus 27% for placebo. From the RCT evidence alone it is clear that CBD isolate is a safe but not especially effective intervention for seizures in LG, Dravet and Tuberous Sclerosis Complex.

As noted by Rawlings[8] there are several limitations of RCTs in assessing evidence for novel medical interventions. For example, the strict inclusion and exclusion criteria of such studies limits the generalisability of findings. This is of particular importance in the case of paediatric-onset intractable epilepsies where the majority of epilepsies diagnosed under the age of 15 are of idiopathic origin[15]. Thus, observational retrospective studies such as ours allow for a wider participation and a broader patient pool to aid in understanding the scope of medical cannabis as an intervention. We acknowledge that retrospective observational research is subject to recall, and this is an inherent limitation of such designs. Given the rarity of such patient populations with these rare forms of epilepsy prospective studies would be very difficult to undertake.

Further, placebo-controlled designs fail to show clinicians the value of the intervention relative to standard AEDs or previous care. Moreover, observational studies allow physicians to understand the prescribing history of patients and reflect the effects of clinical decisions rather than RCT driven research interventions with stringent, mildly clinically translatable and often biasedly selected primary endpoints[16].

There are also significant risk and ethical implications associated with randomising children suffering with epilepsy to placebo arms and delaying their treatment. One meta-analysis of placebo controlled randomised trials with AEDs reported a 7-fold increase in risk of sudden unexpected death in epilepsy (SUDEP) in those randomised to a placebo arm[17].

Current NICE guidance, limiting prescribing for medical cannabis for this patient group to CBD in the form of Epidyolex, has relied on four RCTs in a limited range of diagnoses. Two

of the children in our sample had failed on Epidyolex. For this reason, NICE guidance has recently been updated to clarify that this should not deter clinicians from prescribing off-license medical cannabis products such as the whole-plant cannabis medicines of which our data support for such prescribing.

Limitations

Further research is required to elucidate the mechanisms by which the respective additive constituents of whole-plant products lead to superior clinical results. Several encouraging pre-clinical lines of work highlight the anti-convulsive and neuroprotective roles of several minor phytocannabinoids including CBDV, D9-THCV and CBG[18]. THC exerts its anticonvulsant effects via activation of the CB1 receptor and subsequent modulation of glutamatergic excitatory activity in the brain[19]. Nonetheless, the investigation of the putative anti-convulsant effects of these cannabinoids needs to be investigated in-vivo to gain a full appreciation for their therapeutic efficacy. Whilst we note the difficulty in conducting prospective studies, these could be designed to identify children who are most likely to benefit from medical cannabis and those that are not in order to stratify treatment packages earlier during their disorders. Such a study would serve to ameliorate the current poor prognosis within this severely ill population.

Mitigating risk is the cornerstone of clinical judgement and there are some opponents of the therapeutic use of THC in children and adolescence. Concern over the deleterious effects of whole-plant medical cannabis must be compared with the known iatrogenic effects of mainline AEDs. One randomised clinical trial of phenobarbital when used chronically for seizure prophylaxis found significant impairment of developmental trajectories[20] as well as a large decrease in global IQ and verbal learning[21]. In another double blind RCT valproate was associated with poorer attentional performance compared with other AEDs[22].

Additionally, adverse effects from AEDs are the leading cause of treatment discontinuation and after seizure frequency, the major determinant of impaired health-related quality of life in people suffering with epilepsy.

Finally, in other medical indications, data obtained other than from RCTs can and does get used by medical regulators. A recent systematic review found that between 1999 and 2014 over 76 unique marketing authorisations were granted without RCT results[23]. Very recently one such drug, Zolgensma[24] for the severe paediatric condition Spinal Muscular Atrophy gained approval on a single-arm open label design with 15 patients.

We believe that our data on whole-plant medical cannabis in childhood-onset severe treatment-resistant epilepsy, provides evidence to encourage its introduction into the NHS within current NICE prescribing guidelines. Such a move would be hugely beneficial to the families, who in addition to having the psychological distress of looking after their chronically ill children, have also to cover the crippling financial burden of their medication.

Data Sharing statement

All the Individual participant data will be available after de-identification and is presented in the table of the manuscript for access by researchers or interested parties.

Author's contributions

RRZ, DJN and LDP analysed the data. AKS added sections of medical cannabis. All authors developed the initial manuscript and all authors reviewed and agreed to the final manuscript

Conflicts of Interest

AKS is Head of Research for the charity Drug Science, which receives an unrestricted educational grant from a consortium of medical cannabis companies. RRZ, LDP and DJN declare no competing interests.

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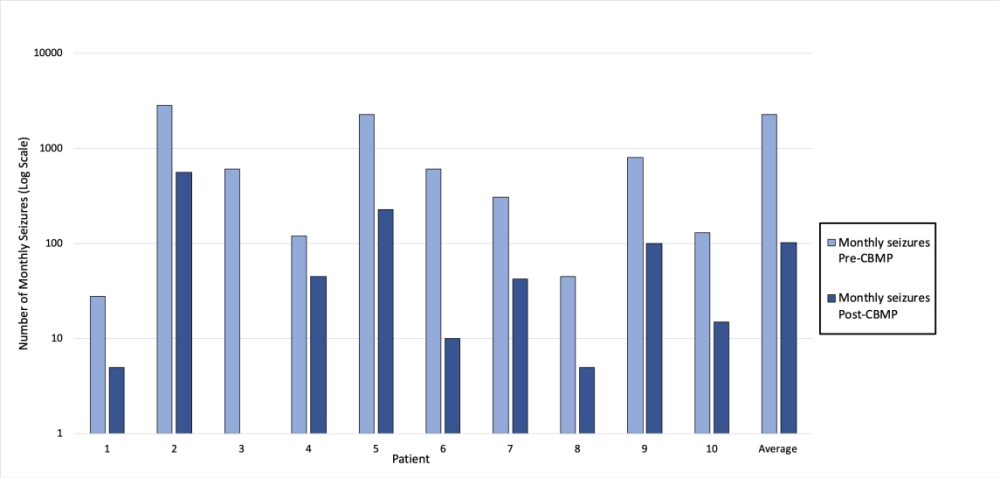

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Medical cannabis for severe treatment resistant epilepsy in children – A case series of ten patients

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Medical cannabis for severe treatment resistant epilepsy in children – A case series of ten patients

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Abstract

Objectives
To report the findings of a case series of ten children suffering with intractable epilepsies in the UK to determine the feasibility for using whole-plant cannabis medicines to treat seizures in children.

Setting
This study was conducted retrospectively through collecting clinical data from caretakers and clinicians on study outcome variables. Participants were recruited through the MedCann Support and End our Pain charity groups which are patient representative groups that support children who are using medical cannabis to treat their epilepsies. Medicines were prescribed to patients by clinicians in both NHS and private medical practices. Follow up calls were conducted throughout the period January 2021 to May 2021 to keep data recorded up to date.

Participants
Ten children, 18 years old or under, with intractable epilepsies were recruited from two charities. There were no limitations on diagnosis, sex or ethnic origin.

Interventions
Participants were treated with a range of whole-plant medical cannabis oils. Individual dosing regimens were determined by clinicians.

Primary outcome measure
The primary outcome measure was seizure frequency

Results
Seizure frequency across all ten participants reduced by 86% with no significant adverse events. Participants reduced use of anti-epileptic drugs from an average of seven to one following treatment with medical cannabis. We also noted significant financial costs of £874 per month to obtain these medicines through private prescriptions.

Conclusions
This study establishes the feasibility of whole-plant medical cannabis as an effective and well-tolerated medicine for reducing seizure frequency in children suffering with intractable epilepsies. These findings justify the potential value of further research into the reported therapeutic benefit of whole-plant medicinal cannabis products

Key words
Epilepsy, Neurology, Paediatric neurology, Clinical Pharmacology, Medical Cannabis, Cannabis based medicinal products (CBMPs)

Key Messages

What is known about the subject?

- Since the 1800s there has been significant anecdotal evidence of the value of medicinal cannabis in treating childhood epilepsies
- There have been 4 successful RCTs showing the therapeutic efficacy of cannabidiol (CBD) for the treatment of Lennox-Gastaut, Dravet's and Tuberous sclerosis syndrome
- There is limited scientific evidence available that has investigated whole-plant cannabis medicines containing THC in paediatric epilepsies.

What does this study add?

- The reduction of seizures demonstrates feasibility for this form of treatment in patients with paediatric intractable epilepsies
- The potential value of further research into the reported therapeutic benefit of whole-plant medicinal cannabis products

Introduction

Though used for millennia in eastern medicine, the advent of medical cannabis as a therapeutic tool to treat seizures in the west was first noted in 1843 by an Irish physician, Dr O'Shaughnessy. He observed that cannabis tinctures resolved seizures in a febrile infant, thus claiming that medicine had found an anticonvulsant of the highest order[1]. In 1971 both recreational and medial cannabis were made illegal in the UK under the Misuse of Drugs Act 1971 and so cannabis research largely ceased. Led by parents whose children had responded well to whole-plant medical cannabis extracts but who had failed on conventional anti-epileptic drugs (AEDs) and purified cannabidiol (Epidiolex), medical cannabis was re-initiated as a medicine in the British pharmacopeia in 2018.

Cannabis-based medical products (CBMPs) comprise a broad range of medicines. They can be plant-based or synthetic and vary from purified single compounds (often THC or CBD) to complex mixtures of hundreds of molecules, in multiple formulations (oils, solutions, sublingual sprays, tablets and capsules), with multiple delivery mechanisms (oral, nasal, rectal, and inhalation)[2].

Of the products licensed in the UK, Epidyolex (licensed for the treatment of epilepsy) is an isolate, Sativex (recommended for spasticity associated with Multiple Sclerosis) comprises a 1:1 CBD:THC isolate ratio, and Nabilone (e.g., used to treat nausea and vomiting due to cancer chemotherapy) is a THC analogue.

A combination of both THC and CBD from whole plant extracts were superior to CBD alone in children suffering from various forms of epilepsy[3].

Despite the change in legal status of medical cannabis, most of these children have not benefited as to date there has been only 3 NHS CBMPs prescriptions made in total and only 2 in children[4]. Many patients are thus forced to resort to private treatment which costs up to £2000 per month[3].

Reasons for this resistance are multifactorial[5,6]. One of the most argued by clinicians who might be prescribers is the lack of evidence for efficacy of medical cannabis. By this they

usually mean that there are no randomised controlled trials (RCTs) that prove efficacy and without these they are not prepared to prescribe. To a lesser extent this has also limited National Institute for Clinical and Healthcare Excellence (NICE) support[7]. It is generally accepted that RCTs though powerful are not the only means to generate evidence for the value of treatments. The previous head of NICE and the Medicines Healthcare Regulatory Agency (MHRA) Sir Michael Rawlins in his 2008 Royal College of Physicians Harveian lecture argued that there are many other ways of collecting useful clinical evidence highlighting:

'Randomised controlled trials, long regarded at the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of 'hierarchies' of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base'[8].

In a recent position statement, NICE declared their willingness to acknowledge additional data sources including 'real world' data and 'relevant data collected outside of the context of traditional trials'[9]. One of these other sources of data, real world evidence (RWE) comes from patient case series with before and after outcome measures. These are particularly useful for conditions where RCTs are unlikely or impossible to perform in examples of rare and idiopathic conditions and especially in paediatric medicine. For this reason, we have conducted an outcome assessment of the use of medical cannabis in 10 children with severe treatment-resistant epilepsy who have all failed on multiple traditional anti-epileptic drugs (AEDs) and many of whom have failed on the licensed cannabidiol (CBD) preparation Epidyolex. Epidyolex is a licensed, pharmaceutical grade, purified CBD medicinal product that is produced by GW Pharma. It is the first and only approved prescription CBD. It is approved to treat seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome or tuberous sclerosis complex (TSC) in patients 1 year of age and over.

Our previous study, an open label retrospective study of the impact of medical cannabis in ten patients found whole plant extracts to be superior to CBD isolate and a mean 80% reduction in seizure frequency in a range of intractable childhood epilepsies where standard treatment had failed[3]. A subsequent qualitative follow-up study highlighted the various benefits patients and their families experienced as a result of treatment with CBMPs[2].

Methods

Study design

We recruited participants through two charities, MedCann Support and End Our Pain, which represent children who are using medical cannabis to treat their intractable epilepsies. At the time of the study there were a total of 40 participants across both charities that were using whole-plant medical cannabis products to treat their epilepsies. The study team liaised with these charities to disseminate the research proposal and participant information sheets to potential participants via the charities email database and social media pages. A total of 26 participants subsequently provided consent for involvement in the study and provided data on study outcome measures (see appendix). Ten of these have been previously reported[3]. Of the remaining 16 participants, only ten participants are involved in this current study. The attrition of six participants were due to missing data (n=5) and being over the age of 18

(n=1). Participants' data were collected from their parents or carers via telephone or video conference calls for the period January 2021 to May 2021.

Study outcomes
The primary study outcome was to assess the percentage change in monthly seizure frequency in participants following initiation of medical cannabis. The secondary study outcomes were to assess the impact of medical cannabis on changes in AED use, to report the concentrations and doses of medical cannabis used by these patients and to document the costs incurred from attaining these prescriptions.

Patient and Public involvement
Participants, parents, and clinicians helped to design the variables and information collected in the study. Working closely with patient groups will ensure the results are disseminated to relevant stakeholders, including patient representative groups and clinical governance bodies.

Participants
We engaged carers of patients, following their consent to engage in the study, to provide information on patients age, diagnoses, current AED's, previous AEDs, previous CBMPs, current CBMPs, monthly seizure frequency pre and post initiation of CBMPs, dose of THC and CBD and cost of CBMPs. Data were confirmed with clinician reports where available.

Study medication
All participants received whole plant extract CBMPs either through private prescription or through the NHS. The CBMPs used included Bedrolite (<1% THC and 9% CBD), Bedica (14% THC and <1% CBD), Celixir 20 (<1% THC and 20% CBD), Sweet pink CBD (<1% THC and 10.6% CBD), Althea 100 (<1% THC and 10% CBD). The prescription of these medicines was initiated by clinicians and all participants continued to use these medicines at the last follow up call. Individual dosing regimens are described in Table 1.

Statistical analysis
Descriptive analysis on group percentage change in seizure outcome are provided. Other variables including mean AED use pre and post initiation of CBMP and mean cost are also described. No significance testing was performed due to no predefined terminal period for data collection.

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

Results

Clinical and demographic details
A total of 10 patients were included in the current study. The mean age of participants was 6.2 years old (range 1-13). All clinical and demographic details can be viewed in table 1.

Table 1: Demographic and clinical data from 10 patients enrolled in the study

Patient	Age	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	% Reduction in monthly seizure frequency	Monthly CBMP Cost

1	6	Epidiloex, Bedrolite, Bedica, Bedrocan, THC-A, Charlottes web	Sweet Pink CBD	2 ml	3.8	200	28	5	82	£1600
2	3	Charlottes Web / Hayleighs Hope / Bedrolite and Bedica	Celixir20	2.2ml	6	225	2,800	560	80	£500
3	7	Epidiolex	Bedrolite	1.4ml	4.2	140	600	0	100	£995.97
4	5	ND	Sweet Pink CBD	1.8ml	5.4	180	120	45	62.5	£200
5	4	ND	Bedrolite	1.2ml	3.6	120	2250	225	90	£1300
6	9	Charlottes webb, Hayleighs hope, over the counter CBD	Bedrolite + Bedrocan	3.6ml Bedrolite	14	360	600	10	98	0
7	13	Bedrolite	Celixir20 and Althea100	0.9 ml Celixir20, 0.2ml Althea100	2.9	110	305	42	86	£1389
8	9	Bedrolite and Bedica	Celixir20	0.75ml	2	75	45	5	89	£400
9	5	ND	Bedrolite	1.4ml	4.2	140	800	100	87.5	£730
10	1	Haleighs Hope	Bedrolite + Bedica	1.68ml Bedrolite, 0.1ml Bedica	5.4	168	130	15	88	£750

Epileptic Aetiologies

The patients presented with a range of epileptic aetiologies including predefined syndromes, rare genetic disorders and undiagnosed epileptic encephalopathies. Two patients presented genetic aetiologies (PCDH19 mutation, chromosome deletion), one with Dravets syndrome, one with Doose syndrome, two with CDKL5 deficiency disorder, one with West syndrome, one with Rett Syndrome, one with Aicardi syndrome and one with undiagnosed refractory epilepsy.

Comorbid diagnosis

Three of the participants presented with multiple comorbid diagnoses. The most reported being Infantile spasms (N=2), learning disabilities (N=1) and global developmental day (N=1)

Medication

Patients reported a mean of 7 (± 4.58) anti-epileptic drugs prior to initiation of CBMPs which reduced to a mean of 1 (± 1.23) per patient with 7 patients managing to completely wean off all AEDs. The most common secondary intervention in the cohort was a ketogenic diet (N=4) prior to initiation of CBMP which was not effective in any patient and was subsequently discontinued. One patient had a current vagal nerve stimulation implant.

Two patients using Epidyolex had failed to respond to this NICE recommended CBMP for treatment resistant epilepsy.

One patient saw a significant worsening of symptoms including an increase in seizure frequency when switching from Bedrolite and Bedica products to other whole-plant CBMPs. The other three patients that changed CBMPs from Bedrolite and Bedica to other products

noted burden of cost as the primary reason for switching product, though all these patients reported the efficacy of Bedrolite and Bedica in reducing seizure frequency.

Seizure frequency
Figure 1 shows the findings from the ten participants enrolled in this case-series. Here we show individual and mean changes in seizure frequency pre and post initiation of CBMP (Note log 10 scale).

The monthly seizure frequency reduced for all 10 patients with an overall mean of 86%.

Insert FIG 1

Figure 1. Monthly seizure frequency pre and post CBMP in ten patients suffering with childhood-onset severe intractable epilepsies

Dose of CBMP
All patients were using whole-plant cannabis products which contain a range of terpenes, flavonoids and minor phytocannabinoids. We are currently in process of analysing the respective components of each medication in this study which we plan to report on. For this study we are only able to report on the respective doses of THC and CBD. For THC dosage, patients consumed a mean (SD) of 5.15(± 6.8) mg of THC a day and for CBD 171.8 (± 153.3) mg of CBD daily.

Cost
The mean cost for participants medical cannabis prescription was £874 per month. One participant had obtained their medical cannabis prescription on the NHS.

Other symptoms
Parents and carers reported significant improvements in health and wellbeing of their children following initiation of whole-plant CBMPs. Particularly, these improvements were noted in sleep, eating, behaviour and cognition. We did not specifically ask for adverse effects here, but in a follow up qualitative study (comprising a subset of eleven of these patients across the current study and our previous one [2,3]) parents were asked about adverse effects specifically. Only few minor adverse effects, such as tiredness before exact dosing were reported. Our patient group almost universally reported highly improved cognitive and behavioural outcomes, likely due both to reduced seizure frequency and reduced use of other AEDs.

Discussion
This study shows the effectiveness of whole-plant medical cannabis in a group of patients suffering with severe intractable childhood-onset epilepsies. The reduction in monthly seizure frequency in our group demonstrates the feasibility for this medication in such patients.

Carers reported sustained and significant improvements in behavioural, psychological and cognitive faculties associated with medical cannabis use.

Our findings are in line with several observational and controlled interventional studies that have seen significant reductions in seizure frequency following treatment with medical cannabis. Moreover, our data suggest that whole-plant medical cannabis products are superior

to isolated CBD products in the patients examined. To date, double-blind placebo controlled RCT evidence is only available for isolate CBD in three rare forms of epilepsy: Lennox Gastaut syndrome (LG), Dravet syndromes and Tuberous Sclerosis complex [10, 11, 12, 13]. One such study showed a reduction of 22.8% in seizures in children with Dravet syndrome[10] while another study by the same author in LG patients using CBD isolate reported a 42% reduction in drop seizures[11]. To expand on this another study [12]conducted a similar double-blind placebo controlled RCT in patients with LG and similarly reported a 44% decrease in drop seizure frequency in the CBD isolate group. A more recent interim analysis of another study[13] sought to examine the effects of add-on CBD isolate to standardised treatment for seizures associated with Tuberous Sclerosis Complex, finding a 48% reduction in seizures versus 27% for placebo. From the RCT evidence alone it is clear that CBD isolate is a safe but not especially effective intervention for seizures in LG, Dravet and Tuberous Sclerosis Complex.

As noted by Rawlings[8] there are several limitations of RCTs in assessing evidence for novel medical interventions. For example, the strict inclusion and exclusion criteria of such studies limits the generalisability of findings. This is of particular importance in the case of paediatric-onset intractable epilepsies where the majority of epilepsies diagnosed under the age of 15 are of idiopathic origin[14]. Thus, observational studies allow for a wider participation and a broader patient pool to aid in understanding the scope of medical cannabis as an intervention. We acknowledge that retrospective observational research is subject to recall, and this is an inherent limitation of such designs. Given the rarity of such patient populations with these forms of epilepsy prospective studies would be challenging and take a long time to complete.

Current NICE guidance, limiting prescribing for medical cannabis for this patient group to CBD in the form of Epidyolex, has relied on four RCTs in a limited range of diagnoses. Two of the children in our sample had failed on Epidyolex. For this reason, NICE guidance has recently been updated to clarify that this should not deter clinicians from prescribing off-license medical cannabis products such as the whole-plant cannabis medicines of which our data support for such prescribing.

Limitations

Our data has number of limitations. First, the data collection was retrospective based on parental recall (though these often-contained seizure diaries). Second, there was no randomisation or placebo and so there was no comparator or placebo group. Thirdly, there may be bias in that the parents that agreed to provide the data were the ones in which the children had had the largest clinical impact from their medical cannabis. Fourthly there was no assessment of the impact of removing the intervention to validate the enduring need for treatment. Finally, the patient number was small, but it did accord with previously reported outcomes in a previous study[3].

Further research is required to elucidate the mechanisms by which the respective additive constituents of whole-plant products lead to superior clinical results. Several encouraging pre-clinical lines of work highlight the anti-convulsive and neuroprotective roles of several minor phytocannabinoids including CBDV, D9-THCV and CBG[15]. THC exerts its anticonvulsant effects via activation of the CB1 receptor and subsequent modulation of glutamatergic excitatory activity in the brain[16]. Nonetheless, the investigation of the putative anti-convulsant effects of these cannabinoids needs to be investigated in-vivo to gain a full appreciation for their therapeutic efficacy. Whilst we note the difficulty in conducting prospective studies, these could be designed to identify children who are most likely to

benefit from medical cannabis and those that are not in order to stratify treatment packages earlier during their disorders. Such a study would serve to ameliorate the current poor prognosis within this severely ill population.

Mitigating risk is the cornerstone of clinical judgement and there are some opponents of the therapeutic use of THC in children and adolescence. Concern over the deleterious effects of whole-plant medical cannabis must be compared with the known iatrogenic effects of mainline AEDs. One randomised clinical trial of phenobarbital when used chronically for seizure prophylaxis found significant impairment of developmental trajectories[17] as well as a large decrease in global IQ and verbal learning[18]. In another double blind RCT valproate was associated with poorer attentional performance compared with other AEDs[19].

Additionally, adverse effects from AEDs are the leading cause of treatment discontinuation and after seizure frequency, the major determinant of impaired health-related quality of life in people suffering with epilepsy. Adverse events are commonly reported with AEDs with one such study reporting 1139 adverse drug reations in 124 young people using antiepileptic drugs[20] while another study reported that behavioural problems and somnolence were the most common adverse drug reactions and that AED polytherapy significantly increase the likelihood of children developing such reactions[21].

We believe that our data on whole-plant medical cannabis in childhood-onset severe treatment-resistant epilepsy, provides evidence to support its introduction into the NHS within current NICE prescribing guidelines. Such a move would be hugely beneficial to the families, who in addition to having the psychological distress of looking after their chronically ill children, have also to cover the crippling financial burden of their medication.

Data Sharing statement

All the Individual participant data will be available after de-identification and is presented in the table of the manuscript for access by researchers or interested parties.

Author's contributions

RRZ, DJN and LDP analysed the data. AKS added sections of medical cannabis. All authors developed the initial manuscript and all authors reviewed and agreed to the final manuscript

Conflicts of Interest

AKS is Head of Research for the charity Drug Science, which receives an unrestricted educational grant from a consortium of medical cannabis companies. RRZ, LDP and DJN declare no competing interests.

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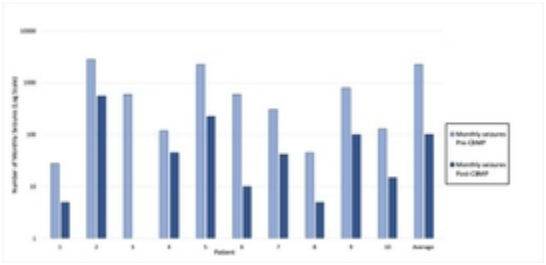

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Appendix A. Interview topic guide

Remind interviewees that this interview is about telling their story, that there are not right or wrong answers, and that they can withdraw from the interview at any time should they wish to or decline to answer a question at any time.

- Can you give us some background to your child's medical cannabis use?
- Can you provide us detail on the following: Age, Diagnosis, Frequency of medical cannabis use, dose of medical cannabis use, company and product of medical cannabis use?
- Can you provide us detail on seizure frequency before medical cannabis use and tell us about the effects of medical cannabis on seizure frequency?
- Could you tell us about your child's previous and current use of anti-epileptic drugs
- Present- what are you are doing now?

- What (if anything) has changed since using medical cannabis?

- What do you like most about the medical cannabis treatment you are receiving?

- What do you dislike most about the medical cannabis treatment you are receiving?

- Can you sum up your thoughts and feelings about the treatment?

- How do previous drugs compare to medical cannabis and/or medical cannabis and other drugs?

- Can you describe the patient's quality of life before and after medical cannabis treatment?

- Can you describe your/your family's quality of life before and after medical cannabis treatment?

- What do your friends and family think about your choice of treatment?

- Future- how do you see your child's future? What are your hopes in terms of medical cannabis treatment?

- What are your worries related to medical cannabis treatment?

- What (if anything) would you like to change about the current approach, e.g. in terms of the medications, regulations, costs, access, etc.?

- Do you feel well provided by your doctor? Does your doctor understand your child's needs in relation to medical cannabis?

- Where would you like to have/have had (more) help and support? From whom?

- What (if anything) has been the impact of COVID-19 on your situation?

- Is there anything you would like to add?

Thank you!