

Abstract

We describe real-world experience with cannabidiol (CBD) in adults with Dravet Syndrome (DS) via GW Pharma early access programme at two UK neurology centres. Adults with genetically-confirmed DS had CBD added to existing therapy, titrated up to 20mg/kg, as tolerated. The primary outcome measure was percentage reduction in convulsive seizures. Secondary outcome measures included changes in myoclonic seizures, and in cognition and quality of life as assessed by the Caregiver Global Impression of Change (CGIC), and incidence of adverse events (AEs). 18 adults (7 female; median age 27.5 years; range 20-51) were included. Median follow-up was 176 days. In one, another antiseizure drug, clobazam, was introduced during the programme. 3/17 (17.6%) had >30% reduction in convulsive seizures (range: 87.5-100%). AEs occurred in all, the most common being transaminitis (52.9%). Behavioural AEs led to discontinuation in 3/18 (16.7%), including a seizure-free responder. In 7/18, CBD was stopped due to lack of effect. 8/18 continue on treatment. Improvements in CGIC were reported in 41.2% and 47.1% by physicians and families, respectively. 17.6% achieved sufficient reduction in convulsive seizure frequency to qualify for NHS funding. AEs led to withdrawal in only 16.7%. Close monitoring and dose adjustments of other antiseizure drugs were necessary.

Keywords: epilepsy; seizures; antiseizure medication

Funding: Part of this work was undertaken at University College London Hospitals, which received a proportion of funding from the NIHR Biomedical Research Centres funding scheme. KS is supported by a Wellcome Trust Strategic Award (WT104033AIA). SB is supported by the Muir Maxwell Trust and the Epilepsy Society. MKS is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Two-centre experience of cannabidiol use in adults with Dravet syndrome

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Introduction

In January 2020, following recommendation from The National Institute for Health and Care Excellence in the UK (NICE) [1], cannabidiol (CBD) was centrally commissioned by NHS England for Lennox-Gastaut and Dravet syndromes (DS) in people over the age of 2 years. Prior to this, CBD became available via GW Pharmaceuticals early access programme (EAP) at certain UK centres. We conducted a prospective audit to assess real-world efficacy and tolerability of CBD in adults with DS at the National Hospital for Neurology and Neurosurgery and King's College Hospitals, London. Our observations may be valuable for physicians considering CBD for adults with DS.

Methods

Patients

This project was reviewed and approved as an observational clinical audit at the participating centres: National Hospital for Neurology and Neurosurgery, London, UK, and King's College Hospital, London UK. No further ethics approval was required.

Only participants with *SCN1A*-mutation confirmed DS were included, to maximise chances of clinically interpretable outcomes from the small EAP allocation. Individuals with highest frequency of generalised tonic clonic seizures were prioritised for inclusion.

All participants underwent screening to collect pre-treatment clinical parameters, including demographics, weight, habitual seizure types, average monthly frequency, and number of previous antiseizure treatments. Level of independence with activities of daily living (ADLs), engagement with activities, understanding of speech, and ability to follow commands facilitated assessment of the Caregiver Global Impression of Change (CGIC) [2].

Early access programme

Treatment was started in all individuals between May and July 2019. CBD oral solution 100mg/ml was introduced at 2.5mg/kg once/day (Centre 1) or twice/day (Centre 2) and increased no quicker than 2.5mg/kg every week up to a ceiling dose of 20mg/kg/day in two divided doses. Changes in doses of other antiseizure medications were avoided unless necessitated by interactions, adverse events or seizure exacerbation.

Outcome measures

As per protocol, patients were assessed in clinic at 3 and 6 months following initiation of CBD. The 6-month assessment was the prespecified end point for outcome assessment. In some individuals, treatment was stopped between clinic appointments, e.g. due to adverse events. In these cases, the endpoint was defined as the date of decision to withdraw the treatment. At Centre 1, for patients continuing treatment beyond the 6-month review, the endpoint was defined as the last clinic review with available outcome data.

The primary outcome measure was percentage reduction in frequency of 'convulsive' seizures (defined in accordance with previous publications [2] as tonic-clonic, tonic and atonic). Baseline seizure frequency was defined as the average monthly number of convulsive seizures over the three months preceding CBD initiation with no other drug changes. For those who required drug changes according to clinical need, a one-month baseline without drug changes was used.

Seizure frequency at the endpoint was defined as monthly frequency, based on a minimum of 1-month observation, or longer, if data on a steady dose were available.

Other seizure-related outcome measures included improvement in frequency of myoclonic seizures.

CGIC was scored separately by the caregiver and by the treating physician.

Blood tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were checked, at a minimum, at baseline and 1, 3 and 6 months after CBD initiation.

All carers were asked to report any adverse effects to us via email as soon as possible to be reported to GW Pharma within 24 hours.

Statistics

Descriptive statistics were performed using Microsoft Excel version 16.38. Due to the small sample size, median and range are reported for continuous variables. The number of previous antiseizure medications was missing from three individuals; they were excluded from analysis for this variable.

Results

Patients

Eighteen adults with DS were treated with CBD (Table 1). All had concomitant therapy with valproate.

11/18 achieved a ceiling dose of 20mg/kg/day; 5/18, 10mg/kg/day; 2/18 discontinued prior to reaching 10mg/kg/day. The median time on the final dose was 78 days. One individual discontinued treatment due to an adverse event 7 days after reaching the final dose. In the remaining individuals, time on the final dose ranged between 21 and 370 days.

Clobazam was introduced during CBD escalation in one person, whose data were therefore excluded from the group analysis. For this person, at last follow-up (6 months after CBD was introduced and 3 months after CLB was introduced) convulsive seizure frequency had improved by > 30%.

Seizure outcome measures

3/17 (17.6%) achieved > 30% reduction in convulsive seizure frequency (range: 87.5-100%). These individuals were aged 27-29. In the individual who became completely seizure-free, CBD was discontinued abruptly without physician consultation due to behavioural side effects. This led to status epilepticus.

Among the 16 patients with myoclonic seizures, improvement with CBD was reported in 5 (31.3%) and deterioration in 2 (11.1%).

Other secondary outcomes

Seven individuals (41.2%) had sustained improvement on physician CGIC. Care-giver CGIC was reported to be improved in 8 (47.1%).

Adverse events

At least one adverse event (AE) was reported in all 17 individuals (Table 1). In all three cases where an AE was the reason for discontinuation, the AE was behavioural/psychiatric.

Derangement of LFTs occurred in over half (all on concomitant valproate), reaching >3 times UNL in 4 (23.5%). None had drug-induced liver injury as defined by concomitant significant increase in bilirubin. Transaminitis resolved completely on VPA dose reduction and slowed CBD titration.

Somnolence was seen in 7 (41.2%). Of these, 3 (42.8%) were on concomitant clobazam. There were two people on clobazam who did not experience somnolence. Desmethylclobazam levels were elevated in two people, one of whom had somnolence. Desmethylclobazam was not measured in all participants. Ammonia levels were not routinely measured. One person with somnolence had an elevated ammonia.

Discussion

Studies to date have described the effects of CBD in children and young adults with DS. Our audit of the efficacy and tolerability of CBD in older adults with DS highlights the complexities associated with CBD use.

In the original efficacy trial in 120 children and young adults with DS, of those treated with CBD at a dose of 20mg/kg/day, 43% achieved a minimum of 50% reduction in frequency of convulsive seizures, compared with 27% of placebo [2]. Similarly, in an uncontrolled expanded access programme, 53% of patients with DS or Lennox-Gastaut syndrome achieved >50% reduction in convulsive seizures, an effect that was sustained in follow up lasting up to 96 weeks [3]. Using the same definition, only 3/17 of our patients (17.6%) were responders. Among the participants of the expanded access programme, only 39% had DS [3]. However, in the RCT, all individuals had DS and comparable baseline frequency of convulsive seizures and previous number of antiepileptic treatments to our patients suggesting similar disease severity [2]. The RCT only included children and young adults [2]. Whilst the expanded access programme included adults up to age 51 as well as children, the mean age was under 13 years [3]. It is possible that our patients' older age and longer duration of epilepsy may have affected response and we note that all three of our responders were in their 20s. The possible effect of age and epilepsy duration on treatment outcomes should be further studied.

Following the publication of the original trial data, a subgroup analysis suggested that the difference in responder rates between CBD and placebo was only statistically significant in the subgroup on clobazam [4]. Consequently, MHRA authorisation and NICE endorsement for CBD was only granted for concomitant use with clobazam [1,4]. Three individuals in our study (17.6%) would have met NICE criteria for continued NHS funding with respect to improvement in seizure frequency. One of them is not on clobazam. A fourth, not included in the analysis, would have fulfilled the criteria, once clobazam was added. 8/18 continue on

treatment, suggesting that the NICE criteria would exclude some patients whose clinicians and relatives consider the improvement worthwhile.

In our relatively short period of observation, we noticed positive effects on cognition, particularly in the language domain, even in the absence of significant reduction in seizures. Care-giver CGIC was reported to be improved in 8 (47.1%). This included six families reporting an improvement in the individual's cognitive abilities and language skills. The changes we observed would have been reflected in the communication domain of the Vineland Adaptive Behaviour Scales [5]. A formal cognitive assessment should be considered in future studies. In four people, there was a reduction in doses of other AEDs that may have contributed to cognitive gains. We note that our study was observational, and neither blinded nor controlled.

Formal trials with the same CBD target dose reported AEs in 78-93% [2,6,7]. All 17 of our patients had at least one AE. Transaminitis has been consistently described with concomitant valproate and, to a lesser extent, clobazam [2,6,7]. All our patients took valproate and transaminitis reversed with adjustments of valproate and slowed CBD escalation. Other important drug-drug interactions (DDIs) include somnolence with co-treatment with clobazam [8]. Three of seven people reporting somnolence were not on clobazam, suggesting this could also be a direct effect of CBD or other DDIs. CBD is also associated with elevations in stiripentol, lamotrigine and phenytoin levels. Awareness of these interactions is essential. We recommend appropriate adjustment of concomitant medication doses when side-effects emerge before further CBD escalation. Where possible, we also recommend monitoring levels of concomitant antiseizure medications at baseline and post CBD initiation.

This small programme was implemented in the context of routine outpatient clinics. Patients' variable geographical location, limited clinic appointment availability and other circumstances

made follow up and monitoring challenging. These factors limit comparability to clinical trials. However, our experience is likely to be generalisable to clinical settings and adults with DS. Our experience supports starting CBD cautiously, especially with concomitant sodium valproate, with slower than recommended dose escalations. We also highlight the importance of an efficient direct communication route to be able to manage abnormal blood test results and AEs effectively.

Conclusion

Caregivers should be counselled about the realistic seizure outcomes expected with CBD and common AEs seen. There should be clarity that continued NHS funding is dependent on sustained improvement of convulsive seizures. Dose adjustments of other medications, particularly, but not exclusively, valproate and clobazam, may be necessary. Our experience highlights the complexities of this treatment and important considerations in the prescribing and monitoring of CBD.

Acknowledgements:

We thank GW Pharma for supplying CBD, and all patients and carers for their participation.

Contributors:

KS: data collection, analysis and drafting of manuscript, LMR, LN: data collection, and interpretation, critical review of manuscript, KH: data collection, critical review of manuscript, SB: data interpretation, critical review of manuscript, SMS: data interpretation, critical review of manuscript, MKS: conception and design, data collection and interpretation, initial critical review, drafting and revision of manuscript.

Declarations of interest:

LN reports personal fees from Advisory Board GW Pharma, outside the submitted work. SMS is a Member of Scientific Advisory Board of Dravet Syndrome UK. The remaining authors: none.

Ethical publication statement:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Data accessibility statement:

Requests for data may be addressed to the corresponding author.

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Tables:

Table 1. Baseline characteristics and outcomes of the CBD Early Access Programme.

Demographics and medications	
Sex	7 (38.9%) female; 11 (61.1%) male
Median age in years (range)	27.5 (20-51)
Median weight in kg (range)	51 (38-82)
Number of regular antiseizure treatments* at baseline (range)	4 (1-5)
Concurrent CLB, n (%)	6 (33%)
Concurrent STP, n (%)	6 (33%)
Number of previous antiseizure treatments* (n=15)	8.5 (4-15)
Habitual seizure types	

Tonic clonic seizures, n (%)	18 (100%)
Tonic and/or atonic seizures, n (%)	9 (50%)
Myoclonic seizures, n (%)	16 (88.9%)
Other seizures, including focal motor and dialeptic, n (%)	10 (55.6%)
Number of convulsive seizures/month at baseline/patient (range)	11.7 (3-75)
Adverse events (n=17)	
Any AE during treatment	17 (100%)
Deranged LFTs	9 (52.9%)
Deranged LFTs>3xUNL	4 (23.5%)
Somnolence/obtundation	7 (41.2%)
Behavioural /psychiatric problems	4 (23.5%)
Diarrhoea	4 (23.5%)
Other (reduced appetite, nausea, refusing medications)	10 (58.8%)
Adverse event outcomes	
CBD withdrawal	3 (17.6%)
CBD dose reduction/slowing of escalation	3 (17.6%)
Changes in other medications	7 (41.2%)
No action	4 (23.5%)
Treatment duration	
CBD duration (days)	176 (38-419)
CBD ongoing at last follow-up (with no plan to withdraw)	8/18 (44.4%)

Main reason for stopping (n=10)	
Lack of response	7 (70%)
Adverse event	3 (30%)

N=18 unless otherwise specified. Abbreviations: CBD – cannabidiol; CLB – clobazam; LFTs – liver function tests; STP – stiripentol; UNL – upper normal limit; VPA – valproate

* Including VNS and ketogenic diet