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(54) **USE OF CANNABINOIDS IN THE TREATMENT OF EPILEPSY**

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(57) **ABSTRACT**

The present disclosure relates to the use of cannabidiol (CBD) for the reduction of total convulsive seizure frequency in the treatment of "treatment-resistant epilepsy" (TRE). In particular, the disclosure relates to the use of CBD of treating TRE when the TRE is Dravet syndrome; myoclonic absence seizures or febrile infection related epilepsy syndrome (FIRES). The disclosure further relates to the use of CBD in combination with one or more anti-epileptic drugs (AEDs).

28 Claims, No Drawings

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USE OF CANNABINOIDS IN THE TREATMENT OF EPILEPSY

This application is a continuation of Ser. No. 15/449,084, filed Mar. 3, 2017, which is a continuation of Ser. No. 15/284,766, filed Oct. 4, 2016, which is a continuation of Ser. No. 14/741,783 filed Jun. 17, 2015, which claims the benefit of priority of GB 1506550.1, filed Apr. 17, 2015, and GB 1410771.8, filed Jun. 17, 2014, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to the use of cannabidiol (CBD) for the reduction of total convulsive seizure frequency in the treatment of "treatment-resistant epilepsy" (TRE). In one embodiment the patients suffering from TRE are children and young adults. CBD appears particularly effective when the TRE is Dravet syndrome; myoclonic absence seizures or febrile infection related epilepsy syndrome (FIRES). In these indications the reduction of total convulsive frequency has surprisingly been shown to be greater than 50%, through 70% to greater than 90% in a significant number of patients. Indeed a significant number of patients have been seizure free at the end of three months treatment.

Preferably the CBD used is in the form of a highly purified extract of *cannabis* such that the CBD is present at greater than 98% of the total extract (w/w) and the other components of the extract are characterised. In particular tetrahydrocannabinol (THC) has been substantially removed to a level of not more than 0.15% (w/w). Alternatively, it is a synthetically produced CBD.

In use the CBD is used concomitantly with one or more other anti-epileptic drugs (AED). Alternatively the CBD may be formulated for administration separately, sequentially or simultaneously with one or more AED or the combination may be provided in a single dosage form. Where the CBD is formulated for administration separately, sequentially or simultaneously it may be provided as a kit or together with instructions to administer the one or more components in the manner indicated.

BACKGROUND TO THE INVENTION

Epilepsy occurs in approximately 1% of the population worldwide, (Thurman et al., 2011) of which 70% are able to adequately control their symptoms with the available existing anti-epileptic drugs (AED). However, 30% of this patient group, (Eadie et al., 2012), are unable to obtain seizure freedom from the AED that are available and as such are termed as suffering from "treatment-resistant epilepsy" (TRE).

Treatment-resistant epilepsy was defined in 2009 by the International League Against Epilepsy (ILAE) as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan et al., 2009).

Individuals who develop epilepsy during the first few years of life are often difficult to treat and as such are often termed treatment-resistant. Children who undergo frequent seizures in childhood are often left with neurological damage which can cause cognitive, behavioral and motor delays.

Childhood epilepsy is a relatively common neurological disorder in children and young adults with a prevalence of approximately 700 per 100,000. This is twice the number of epileptic adults per population.

When a child or young adult presents with a seizure, investigations are normally undertaken in order to investigate the cause. Childhood epilepsy can be caused by many different syndromes and genetic mutations and as such diagnosis for these children may take some time.

One such childhood epilepsy is Dravet syndrome. Onset of Dravet syndrome almost always occurs during the first year of life with clonic and tonic-clonic seizures in previously healthy and developmentally normal infants (Dravet, 2011). Symptoms peak at about five months of age. Other seizures develop between one and four years of age such as prolonged focal dyscognitive seizures and brief absence seizures.

Seizures progress to be frequent and treatment-resistant, meaning that the seizures do not respond well to treatment. They also tend to be prolonged, lasting more than 5 minutes. Prolonged seizures may lead to status epilepticus, which is a seizure that lasts more than 30 minutes, or seizures that occur in clusters, one after another.

Prognosis is poor and approximately 14% of children die during a seizure, because of infection, or suddenly due to uncertain causes, often because of the relentless neurological decline. Patients develop intellectual disability and lifelong ongoing seizures. Intellectual impairment varies from severe in 50% patients, to moderate and mild intellectual disability each accounting for 25% of cases.

There are currently no FDA approved treatments specifically indicated for Dravet syndrome. The standard of care usually involves a combination of the following anticonvulsants: clobazam, clonazepam, levetiracetam, topiramate and valproic acid.

Stiripentol is approved in Europe for the treatment of Dravet syndrome in conjunction with clobazam and valproic acid. In the US, stiripentol was granted an Orphan Designation for the treatment of Dravet syndrome in 2008; however, the drug is not FDA approved.

Potent sodium channel blockers used to treat epilepsy actually increase seizure frequency in patients with Dravet Syndrome. The most common are phenytoin, carbamazepine, lamotrigine and rufinamide.

Management may also include a ketogenic diet, and physical and vagus nerve stimulation. In addition to anticonvulsive drugs, many patients with Dravet syndrome are treated with anti-psychotic drugs, stimulants, and drugs to treat insomnia.

Common AED defined by their mechanisms of action are described in the following tables:

Examples of Narrow Spectrum AED

Narrow-spectrum AED	Mechanism
Phenytoin	Sodium channel
Phenobarbital	GABA/Calcium channel
Carbamazepine	Sodium channel
Oxcarbazepine	Sodium channel
Gabapentin	Calcium channel
Pregabalin	Calcium channel
Lacosamide	Sodium channel
Vigabatrin	GABA

Examples of Broad Spectrum AED

Broad-spectrum AED	Mechanism
Valproic acid	GABA/Sodium channel
Lamotrigine	Sodium channel
Topiramate	GABA/Sodium channel
Zonisamide	GABA/Calcium/Sodium channel
Levetiracetam	Calcium channel
Clonazepam	GABA
Rufinamide	Sodium channel

Examples of AED Used Specifically in Childhood Epilepsy

AED	Mechanism
Clobazam	GABA
Stiripentol	GABA

Over the past forty years there have been a number of animal studies on the use of the non-psychoactive cannabinoid cannabidiol (CBD) to treat seizures. For example, Consroe et al., (1982) determined that CBD was able to prevent seizures in mice after administration of pro-convulsant drugs or an electric current.

Studies in epileptic adults have also occurred in the past forty years with CBD. Cunha et al. reported that administration of CBD to eight adult patients with generalized epilepsy resulted in a marked reduction of seizures in 4 of the patients (Cunha et al., 1980).

A study in 1978 provided 200 mg/day of pure CBD to four adult patients, two of the four patients became seizure free, whereas in the remainder seizure frequency was unchanged (Mechoulam and Carlini, 1978).

In contrast to the studies described above, an open label study reported that 200 mg/day of pure CBD was ineffective in controlling seizures in twelve institutionalized adult patients (Ames and Cridland, 1986).

Based on the fact that chronologically the last study to look at the effectiveness of CBD in patients with epilepsy proved that CBD was unable to control seizures, there would be no expectation that CBD might be useful as an anti-convulsant agent.

In the past forty years of research there have been over thirty drugs approved for the treatment of epilepsy none of which are cannabinoids. Indeed, there appears to have been a prejudice against cannabinoids, possible due to the scheduled nature of these compounds and/or the fact that THC, which is a known psychoactive, has been ascribed as a pro-convulsant (Consroe et al., 1977).

A paper published recently suggested that cannabidiol-enriched *cannabis* may be efficacious in the treatment of epilepsy. Porter and Jacobson (2013) report on a parent survey conducted via a Facebook group which explored the use of *cannabis* which was enriched with CBD in children with treatment-resistant epilepsy. It was found that sixteen of the 19 parents surveyed reported an improvement in their child's epilepsy. The children surveyed for this paper were all taking *cannabis* that was purported to contain CBD in a high concentration although the amount of CBD present and the other constituents including THC were not known. Indeed, whilst CBD levels ranged from 0.5 to 28.6 mg/kg/day (in those extracts tested), THC levels as high as 0.8 mg/kg/day were reported.

Providing children with TRE with a *cannabis* extract that comprises THC, which has been described as a pro-convulsant (Consroe et al., 1977), in even small amounts, let alone at a potentially psychoactive dose of 0.8 mg/kg/day, is extremely dangerous and as such there is a real need to determine whether CBD is in fact efficacious.

To date there have been no controlled trials of CBD in children and young adults with TRE.

BRIEF SUMMARY OF THE DISCLOSURE

In accordance with a first aspect of the present invention there is provided cannabidiol (CBD) for use in the treatment of treatment-resistant epilepsy (TRE), wherein the epilepsy is febrile infection related epilepsy syndrome (FIRES).

In accordance with a second aspect of the present invention there is provided cannabidiol (CBD) for use in the treatment of epilepsy, wherein the epilepsy is a treatment-resistant epilepsy (TRE), and wherein the CBD is present in an amount that reduces total convulsive seizure frequency by greater than 50% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED).

Preferably the CBD is used in combination with two or more concomitant anti-epileptic drugs (AED). The CBD may be formulated for administration separately, sequentially or simultaneously with one or more AED or the combination may be provided in a single dosage form.

Preferably the seizure type to be treated is a complex partial seizure (focal seizure with impairment).

Preferably the CBD is present in an amount that reduces total convulsive seizure frequency by greater than 70% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED). More preferably the CBD is present in an amount that reduces total convulsive seizure frequency by greater than 90% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED). More preferably still the CBD is present in an amount that reduces total convulsive seizure frequency by 100% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED).

In one embodiment the CBD is present as a highly purified extract of *cannabis* which comprises at least 98% (w/w) CBD.

The one or more AED is preferably selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

Preferably the CBD is used in combination with clobazam.

Preferably the number of different anti-epileptic drugs or the dose of AED that are used in combination with the CBD is reduced. More preferably the dose of AED which is reduced is of clobazam.

Preferably the dose of CBD is greater than 5 mg/kg/day. Thus for a 15 kg patient a dose of greater than 75 mg of CBD per day would be provided. Doses greater than 5 mg/kg/day such as greater than 10/mg/kg/day, greater than 15 mg/kg/day, greater than 20 mg/kg/day and greater than 25 mg/kg/day are also envisaged to be effective.

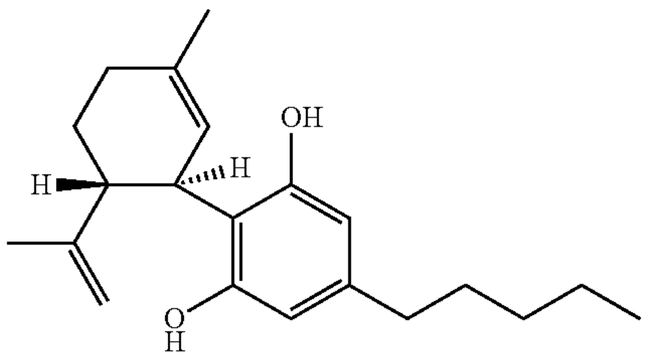
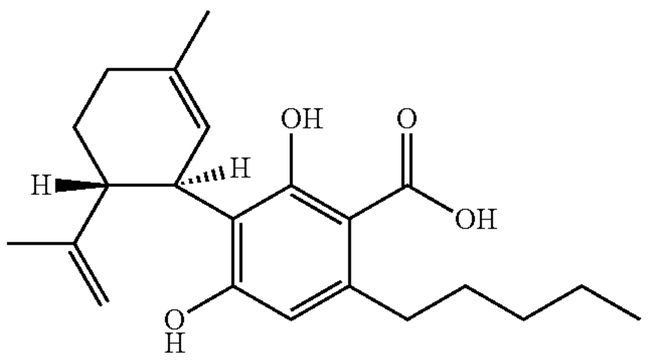
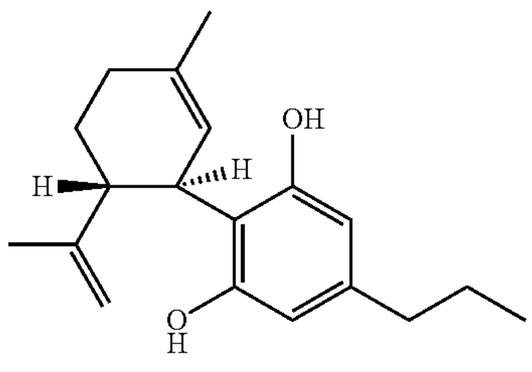
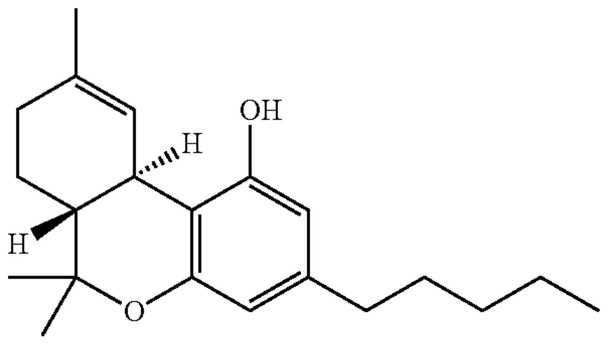
In accordance with a third aspect of the present invention there is provided a method of treating treatment-resistant epilepsy comprising administering cannabidiol (CBD) to a subject, wherein the epilepsy is febrile infection related epilepsy syndrome (FIRES).

In accordance with a fourth aspect of the present invention there is provided a method of treating treatment-resistant epilepsy comprising administering cannabidiol (CBD) to a subject in an amount sufficient to reduce total convulsive seizure frequency by greater than 50% with respect to the seizure frequency achieved on one or more concomitant anti-epileptic drugs (AED).

Definitions

Definitions of some of the terms used to describe the invention are detailed below:

The cannabinoids described in the present application are listed below along with their standard abbreviations.

CBD	Cannabidiol	
CBDA	Cannabidiolic acid	
CBDV	Cannabidivarin	
THC	Tetrahydrocannabinol	

The table above is not exhaustive and merely details the cannabinoids which are identified in the present application for reference. So far over 60 different cannabinoids have been identified and these cannabinoids can be split into different groups as follows: Phytocannabinoids; Endocannabinoids and Synthetic cannabinoids (which may be novel cannabinoids or synthetically produced phytocannabinoids or endocannabinoids).

"Phytocannabinoids" are cannabinoids that originate from nature and can be found in the *cannabis* plant. The phytocannabinoids can be isolated from plants to produce a highly purified extract or can be reproduced synthetically.

"Highly purified cannabinoids" are defined as cannabinoids that have been extracted from the *cannabis* plant and purified to the extent that other cannabinoids and non-cannabinoid components that are co-extracted with the cannabinoids have been removed, such that the highly purified cannabinoid is greater than or equal to 98% (w/w) pure.

"Synthetic cannabinoids" are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.

Phytocannabinoids can be obtained as either the neutral (decarboxylated form) or the carboxylic acid form depending on the method used to extract the cannabinoids. For example it is known that heating the carboxylic acid form will cause most of the carboxylic acid form to decarboxylate into the neutral form.

"Treatment-resistant epilepsy" (TRE) is defined as per the ILAE guidance of 2009 as epilepsy that is not adequately controlled by trials of one or more AED.

"Childhood epilepsy" refers to the many different syndromes and genetic mutations that can occur to cause epilepsy in childhood. Examples of some of these are as follows: Dravet Syndrome; Myoclonic-Absence Epilepsy; Lennox-Gastaut syndrome; Generalized Epilepsy of

unknown origin; CDKL5 mutation; Aicardi syndrome; bilateral polymicrogyria; Dup15q; SNAP25; and febrile infection related epilepsy syndrome (FIRES); benign rolandic epilepsy; juvenile myoclonic epilepsy; infantile spasm (West syndrome); and Landau-Kleffner syndrome. The list above is non-exhaustive as many different childhood epilepsies exist.

DETAILED DESCRIPTION

Preparation of Highly Purified CBD Extract

The following describes the production of the highly-purified (>98% w/w) cannabidiol extract which has a known and constant composition which was used for the expanded access trials described in Examples below.

In summary the drug substance used in the trials is a liquid carbon dioxide extract of high-CBD containing chemotypes of *Cannabis sativa* L. which had been further purified by a solvent crystallization method to yield CBD. The crystallisation process specifically removes other cannabinoids and plant components to yield greater than 98% CBD.

The *Cannabis sativa* L. plants are grown, harvested, and processed to produce a botanical extract (intermediate) and then purified by crystallization to yield the CBD (drug substance).

The plant starting material is referred to as Botanical Raw Material (BRM); the botanical extract is the intermediate; and the active pharmaceutical ingredient (API) is CBD, the drug substance.

Both the botanical starting material and the botanical extract are controlled by specifications. The drug substance specification is described in Table 1 below.

TABLE 1

CBD Specification

Test	Test Method	Limits
Appearance	Visual	Off-white/pale yellow crystals
Identification A	HPLC-UV	Retention time of major peak corresponds to certified CBD Reference Standard
Identification B	GC-FID/MS	Retention time and mass spectrum of major peak corresponds to certified CBD Reference Standard
Identification C	FT-IR	Conforms to reference spectrum for certified CBD Reference Standard
Identification D	Melting Point	65-67° C.
Identification E	Specific Optical Rotation	Conforms with certified CBD Reference Standard; −110° to −140° (in 95% ethanol)
Total Purity	Calculation	≥98.0%
Chromatographic Purity 1	HPLC-UV	≥98.0%
Chromatographic Purity 2	GC-FID/MS	≥98.0%
Impurities (Other Cannabinoids):	HPLC-UV	
CBDA		NMT 0.15% w/w
CBDV		NMT 1.0% w/w
Δ^9 THC		NMT 0.15% w/w
CBD-C4		NMT 0.5% w/w
Residual Solvents:	GC	
Alkane		NMT 0.5% w/w
Ethanol		NMT 0.5% w/w
Residual Water	Karl Fischer	NMT 1.0% w/w

NMT—Not more than

The purity of the CBD drug substance achieved is greater than 98%. The possible impurities are related cannabinoids: CBDA, CBDV, CBD-C4 and THC.

Distinct chemotypes of *Cannabis sativa* L. plant have been produced to maximize the output of the specific chemical constituents, the cannabinoids. One type of plant produces predominantly CBD. Only the (−)-trans isomer occurs naturally, furthermore during purification the stereochemistry of CBD is not affected.

Production of the Intermediate

An overview of the steps to produce a botanical extract, the intermediate, are as follows:

1. Growing
2. Decarboxylation
3. Extraction No. 1—using liquid CO_2
4. Extraction No. 2—'winterization' using ethanol
5. Filtration
6. Evaporation

High CBD chemovars were grown, harvested and dried and stored in a dry room until required. The botanical raw material (BRM) was finely chopped using an Apex mill fitted with a 1 mm screen. The milled BRM was stored in a freezer for up to 3 months prior to extraction.

Decarboxylation of CBDA to CBD was carried out using a large Heraeus tray oven. The decarboxylation batch size in the Heraeus is approximately 15 Kg. Trays were placed in the oven and heated to 105° C.; the BRM took 96.25 minutes to reach 105° C. Held at 105° C. for 15 Minutes. Oven then set to 150° C.; the BRM took 75.7 minutes to reach 150° C.; BRM held at 150° C. for 130 Minutes. Total time in the oven was 380 Minutes, including 45 minutes cooling and 15 Minutes venting.

Extraction No 1 was performed using liquid CO_2 at 60 bar/10° C. to produce botanical drug substance (BDS) which was used for crystallisation to produce the test material.

The crude CBD BDS was winterised in Extraction No 2 under standard conditions (2 volumes of ethanol at minus 20° C. for around 50 hours). The precipitated waxes were

removed by filtration and the solvent evaporated using the rotary evaporator (water bath up to 60° C.) to yield the BDS.

Production of the Drug Substance

The manufacturing steps to produce the drug substance from the intermediate botanical extract are as follows:

1. Crystallization using C5-C12 straight chain or branched alkane
2. Filtration
3. Optional recrystallization from C5-C12 straight chain or branched alkane
4. Vacuum drying

Intermediate botanical extract (12 kg) produced using the methodology above was dispersed in C5-C12 straight chain or branched alkane (9000 ml, 0.75 vols) in a 30 litre stainless steel vessel.

The mixture was manually agitated to break up any lumps and the sealed container then placed in a freezer for approximately 48 hours.

The crystals were isolated by vacuum filtration, washed with aliquots of cold C5-C12 straight chain or branched alkane (total 12000 ml), and dried under a vacuum of <10 mb at a temperature of 60° C. until dry before submitting the drug substance for analysis.

The dried product was stored in a freezer at minus 20° C. in a pharmaceutical grade stainless steel container, with FDA food grade approved silicone seal and clamps.

Examples 1 to 3 below describe the use of a highly purified *cannabis* extract comprising cannabidiol (CBD). Cannabidiol is the most abundant non-psychoactive cannabinoid in the *cannabis* plant. Previous studies in animals have demonstrated that CBD has anticonvulsant efficacy in multiple species and models.

Example 1 describes data produced in an expanded access treatment program in children with TRE.

Examples 2 to 4 demonstrates the efficacy of CBD in children with Dravet syndrome, myoclonic absence seizures and FIRES respectively.

Example 1: Efficacy of Cannabidiol in Children and Young Adults with Treatment-Resistant Epilepsy

Materials and Methods

Twenty-seven children and young adults with severe, childhood onset treatment-resistant epilepsy (TRE) were tested with a highly purified extract of cannabidiol (CBD) obtained from a *cannabis* plant. The participants in the study were part of an expanded access compassionate use program for CBD.

All patients entered a baseline period of 4 weeks when parents/caregivers kept prospective seizure diaries, noting all countable motor seizure types.

The patients then received a highly purified CBD extract (greater than 98% CBD w/w) in sesame oil, of known and constant composition, at a dose of 5 mg/kg/day in addition to their baseline anti-epileptic drug (AED) regimen.

The daily dose was gradually increased by 2 to 5 mg/kg increments until intolerance occurred or a maximum dose of 25 mg/kg/day was achieved.

Patients were seen at regular intervals of 2-4 weeks. Laboratory testing for hematologic, liver, kidney function, and concomitant AED levels was performed at baseline, and after 4, 8 and 12 weeks of CBD therapy.

Results

There were 27 children and young adult patients who received at least 3 months of treatment all of whom suffered from treatment-resistant epilepsy.

All patients were taking at least two concomitant anti-epileptic drugs. These included clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide. The average number of concomitant anti-epileptic drugs being taken was 2.7. The majority took either clobazam and/or valproic acid.

Co-treatment of CBD with clobazam was a significant predictor of a positive treatment response of greater than 50% responder rate. There was an odds ratio (OR) of 3.3 for total seizure reduction and of 1.9 for convulsive seizures. The OR evaluates whether the odds of a certain event or outcome is the same for two groups. Specifically, the OR measures the ratio of the odds that an event or result will occur to the odds of the event not happening. An OR greater than 1 signifies that patients treated with a combination of CBD with clobazam will have a better odds of having a positive reduction in seizures than if they were not taking this combination of medications.

The median number of seizures that these patients suffered from before starting treatment was 30 seizures per month, with a range of 4 to 2,800 seizures per month being recorded.

Efficacy results for the 27 patients are summarized in Table 2 below.

TABLE 2

Changes in Seizure Frequency with CBD Therapy

All patients	Month 3 (n = 27)
Responder rate (>50% reduction) [%]	13 [48%]
Responder rate (>70% reduction) [%]	11 [41%]
Responder rate (>90% reduction) [%]	6 [22%]
Seizure free [%]	2 [7%]

Table 2 shows that after 3 months of therapy, 48% of patients had an equal to or greater than >50% reduction in seizures.

Remarkably, two of the patients, equating to 7%, were entirely free from seizures at the three month stage.

None of the 27 subjects withdrew during the 3-month treatment period and adverse events were mild and well tolerated. Common adverse events included somnolence, fatigue, decreased appetite, increased appetite and diarrhea.

In five subjects their dose of clobazam was reduced due to its sedative effect.

Conclusions

These preliminary results indicate that CBD significantly reduces the number of seizures in a high proportion of patients that do not respond well to existing AED. The cannabidiol was generally well-tolerated in doses up to 25 mg/kg/day.

It was surprising that in this group of patients which are treatment-resistant such a high number were able to gain an effect. The fact that nearly half of the patients (48%) benefited from at least a fifty percent reduction in the number of seizures that they suffered from was remarkable.

Furthermore, nearly a quarter (22%) of patients whose seizures were not controlled with at least two anti-epileptic drugs, experienced a reduction of 90% of the number of seizures they were experiencing and 7% were completely seizure free at the end of the 3 month trial period.

Even more remarkable were the results for some defined sub-sets of this generic group and these are set out on Examples 2 to 4 below.

Example 2: Efficacy of Cannabidiol in Children and Young Adults with Treatment Resistant Dravet Syndrome

Materials and Methods

Nine children and young adults with treatment-resistant Dravet syndrome were part of an expanded access compassionate use program for highly purified CBD extract as described in Example 1.

Results

All nine patients with Dravet syndrome were taking at least two concomitant anti-epileptic drugs. These were largely AED operating via GABA and included clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; and zonisamide. The average number of concomitant antiepileptic drugs being taken was 2.7.

The mean number of seizures that these patients suffered from before starting treatment was 35 seizures per month, with a range of 6 to 112 seizures per month recorded.

Efficacy results for the 9 patients are summarized in Table 3 below.

TABLE 3

Changes in Seizure Frequency with CBD Therapy in Dravet Syndrome patients

	Dravet patients (n = 9)	All patients (n = 27)	All patients excluding Dravet patients (n = 18)
Responder rate (>50% reduction) [%]	5 [56%]	13 [48%]	8 [44%]
Responder rate (>70% reduction) [%]	4 [44%]	11 [41%]	7 [39%]
Responder rate (>90% reduction) [%]	3 [33%]	6 [22%]	3 [17%]
Seizure free [%]	2 [22%]	2 [7%]	0

Table 3 shows that after 3 months of therapy, 56% of patients had an equal to or greater than 50% reduction in seizures, a third had a 90% reduction and remarkably 22%, were entirely free from seizures at the three month stage.

None of the 9 subjects withdrew during the 3-month treatment period and adverse events were mild and well tolerated. Common adverse events included somnolence, fatigue, decreased appetite, increased appetite and diarrhea.

Conclusions

These data demonstrate that in this sub-group of patients with treatment-resistant Dravet syndrome a surprisingly high number were able to gain a dramatic reduction in the number of seizures.

Nearly a quarter (22%) of patients were entirely seizure free at the end of the 3 month trial period. This would not be expected in this group of patients who were taking a large number of different anti-epileptic medications and yet were still suffering from a large number of seizures per day.

Example 3: Efficacy of Cannabidiol in Children and Young Adults with Treatment Resistant Myoclonic Absence Seizures

Materials and Methods

Four children and young adults with treatment-resistant myoclonic absence seizures were part of an expanded access compassionate use program for highly purified CBD extract as described in Example 1.

Results

All four patients with myoclonic absence seizures were taking at least two concomitant anti-epileptic drugs. These were largely AED operating via GABA and included clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; and zonisamide. The average number of concomitant antiepileptic drugs being taken was 2.7.

Efficacy results for the four patients are summarized in Table 4 below.

TABLE 4

Changes in Seizure Frequency with CBD Therapy in patients with myoclonic absence seizures (MAS)

	MAS patients (n = 4)	All patients (n = 27)	All patients excluding MAS patients (n = 23)
Responder rate (>50% reduction) [%]	2 [50%]	13 [48%]	11 [48%]
Responder rate (>70% reduction) [%]	2 [50%]	11 [41%]	9 [39%]
Responder rate (>90% reduction) [%]	1 [25%]	6 [22%]	5 [22%]
Seizure free [%]	0	2 [7%]	2 [9%]

Table 4 shows that after 3 months of therapy, half of the patients had an equal to or greater than 50% reduction in seizures, one patient (25%) had a 90% reduction at the three month stage.

None of the 4 subjects withdrew during the 3-month treatment period and adverse events were mild and well tolerated. Common adverse events included somnolence, fatigue, decreased appetite, increased appetite and diarrhea.

Conclusions

These data demonstrate that in this sub-group of patients with treatment-resistant MAS a surprisingly high number were able to gain a reduction in the number of seizures.

Example 4: Efficacy of Cannabidiol in Children with Treatment Resistant Febrile Infection Related Epilepsy Syndrome (FIRES)

Febrile Infection Related Epilepsy Syndrome (FIRES) is a catastrophic epileptic encephalopathy with an unidentified aetiology that comprises a small minority of all patients with refractory status epilepticus.

This syndrome occurs in previously healthy children with 66-100% of survivors becoming developmentally disabled. The mortality rate is up to 30%. There is a critical need for new therapies to treat this condition.

Materials and Methods

Three patients with FIRES, with an age range of from 4 to 15 years, were treated with CBD under an expanded access program as described previously in Example 1.

Safety laboratory studies, physical/neurological exams, 24 hour video/EEG and seizure types and frequencies were assessed at baseline and one month after starting CBD.

A highly purified extract of CBD as an oral solution in sesame oil was used at a concentration of 25 mg/mL.

Treatment was initiated at a dose of 10 mg/kg/day given in two divided doses, increasing by 5 mg/kg/day every 3 days.

Following seizure improvement an average of 2 AEDs were weaned.

Results

Prior to initiation of treatment with highly purified CBD, the patients all suffered from refractory seizures or status epilepticus. These had been treated with anaesthetics including midazolam infusion, pentobarbital infusion, propofol infusion, and isofluorane infusion, additionally patients also were given steroids including lidocaine infusion, and methylprednisolone and other treatments including ketamine,

fosphenytoin, thiamine, rituximab, cyclophosphamide, intravenous immunoglobulin, and a hypothermia protocol.

At the time of initiation of CBD, the patients were taking between three and five anti-epileptic drugs including: levetiracetam, clobazam, perampanel, phenobarbital, phenytoin, carbamezapine, felbamate, ketogenic diet, lamotrigine, valproic acid and vagus nerve stimulation therapy.

Baseline 24 hour EEG of seizures were recorded. The total seizures at baseline and during the treatment period are shown in Table 5. Patient 1 was shown to be seizure free after starting treatment for almost all of the treatment period, with the number of seizures being reduced from 7 to 0.3 over a 24 week period. Patient 2 had a 50% reduction in seizures after 4 weeks however the seizure frequency increased after a further 4 weeks then started to decrease again after 16 weeks of treatment. The most remarkable response was seen in Patient 3, who suffered from 5600 seizures at baseline. The number of seizures were dramatically reduced after 4 weeks and at week 24 this patient was still demonstrating a greater than 90% reduction in the number of seizures.

The type of seizures that occurred in the three FIRES patients were all complex partial seizures (focal seizures with impairment). None of the FIRES patients suffered from focal seizures with secondary generalisation or convulsive seizures.

TABLE 5

Total Seizure Data

Visit	Frequency (per month)	Change from Baseline	% Change from Baseline	Responder (>=50% Reduction)	Responder (>=70% Reduction)	Responder (>=90% Reduction)	Seizure Free
Patient 1							
BL	4.0	n/a	n/a	n/a	n/a	n/a	n/a
Wk 4	0.0	−4.0	−100.0	Yes	Yes	Yes	Yes
Wk 8	1.0	−3.0	−75.0	Yes	Yes	No	No
Wk 12	0.0	−4.0	−100.0	Yes	Yes	Yes	Yes
Wk 16	0.0	−4.0	−100.0	Yes	Yes	Yes	Yes
Wk 24	0.3	−3.7	−92.0	Yes	Yes	Yes	No
Patient 2							
BL	7.0	n/a	n/a	n/a	n/a	n/a	n/a
Wk 2	0.8	−6.2	−88.6	Yes	Yes	No	No
Wk 4	3.0	−4.0	−57.1	Yes	No	No	No
Wk 8	10.0	3.0	42.9	No	No	No	No
Wk 12	8.0	1.0	14.3	No	No	No	No
Wk 16	4.0	−3.0	−42.9	No	No	No	No
Patient 3							
BL	5600.0	n/a	n/a	n/a	n/a	n/a	n/a
Wk 4	47.2	−5552.8	−99.2	Yes	Yes	Yes	No
Wk 8	9.2	−5590.8	−99.8	Yes	Yes	Yes	No
Wk 12	141.6	−5458.4	−97.5	Yes	Yes	Yes	No
Wk 24	542.0	−5058.0	−90.3	Yes	Yes	Yes	No

Follow up laboratory tests showed no changes in safety studies or concomitant AED levels. No treatment related adverse effects were observed.

Conclusions

CBD treatment was very well tolerated and associated with a dramatic and nearly immediate greater than 90% improvement in clinical and electrographic seizure burden in two of the three children with refractory seizures or status epilepticus due to FIRES.

After a reduction in seizures the patients were able to walk and verbalize once more.

SUMMARY TABLE AND CONCLUSIONS

Table 6 below summarises the data obtained in the three sub-sets: Dravet syndrome; myoclonic absence seizures (MAS) and febrile infection related epilepsy syndrome (FIRES) after 12 weeks of treatment which have been described in the Examples 2 to 4 above. In addition the data for the remainder of the patients with other epilepsy syndromes are detailed. These data which exclude the patients with Dravet, MAS and FIRES show a far lower responder rate than for the specified sub-sets of the above specified sub-sets of epilepsy.

In particular, the responder rate for patients obtaining a greater than 90% reduction in their seizures is reduced from 33% in Dravet patients to only 8% in the unspecified group. This suggests that patients suffering from a TRE of sub-type Dravet syndrome, myoclonic absence seizures or FIRES will respond better to treatment with highly purified CBD than patients with other epilepsy sub-types.

TABLE 6

Changes in Seizure Frequency with CBD Therapy in patients with sub-type TRE and all patients excluding the sub-types.

	All patients (excluding Dravet, MAS and FIRES) (n = 13)	Dravet patients (n = 9)	MAS patients (n = 4)	FIRES patients (n = 3)
Responder rate (>50% reduction) [%]	5 [38%]	5 [56%]	2 [50%]	2 [67%]
Responder rate (>70% reduction) [%]	4 [31%]	4 [44%]	2 [50%]	2 [67%]

TABLE 6-continued

Changes in Seizure Frequency with CBD Therapy in patients with sub-type TRE and all patients excluding the sub-types.

	All patients (excluding Dravet, MAS and FIRES) (n = 13)	Dravet patients (n = 9)	MAS patients (n = 4)	FIRES patients (n = 3)
Responder rate (>90% reduction) [%]	1 [8%]	3 [33%]	1 [25%]	2 [67%]
Seizure free [%]	0	2 [22%]	0	1 [33%]

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The invention claimed is:

1. A method of treating seizures in a patient with treatment-resistant Lennox-Gastaut syndrome, comprising administering to the patient in need thereof cannabidiol (CBD), wherein the CBD has a purity of at least 98% (w/w) CBD, and wherein the CBD is administered at a dose of 5 mg/kg/day, and then the dose is increased by 2 to 5 mg/kg increments.

2. The method of claim **1**, wherein the administering reduces total convulsive seizure frequency.

3. The method of claim **1**, wherein the dose of the CBD is increased to about 10 mg/kg/day to about 25 mg/kg/day.

4. The method of claim **1**, wherein the dose of the CBD is increased to about 15 mg/kg/day to about 25 mg/kg/day.

5. The method of claim **1**, wherein the dose of the CBD is increased to about 25 mg/kg/day.

6. The method of claim **1**, wherein the dose of the CBD is increased to about 10 mg/kg/day.

7. The method of claim **1**, wherein the dose of the CBD is increased to about 12 mg/kg/day.

8. The method of claim **1**, wherein the dose of the CBD is increased to about 14 mg/kg/day.

9. The method of claim **1**, wherein the dose of the CBD is increased to about 15 mg/kg/day.

10. The method of claim **1**, wherein the dose of the CBD is increased to about 18 mg/kg/day.

11. The method of claim **1**, wherein the dose of the CBD is increased to about 20 mg/kg/day.

12. The method of claim **1**, further comprising administering clobazam to the patient.

13. A method of reducing convulsive seizure frequency in a patient with treatment-resistant Lennox-Gastaut syndrome, comprising administering to the patient in need thereof cannabidiol (CBD), wherein the CBD has a purity of at least 98% (w/w) CBD, wherein the dose of the CBD is 5 mg/kg/day to 25 mg/kg/day.

14. A method of reducing convulsive seizure frequency in a patient with treatment-resistant Dravet syndrome, comprising administering to the patient in need thereof cannabidiol (CBD), wherein the CBD has a purity of at least 98% (w/w) CBD, wherein the dose of the CBD is 5 mg/kg/day to 25 mg/kg/day.

15. The method of claim **1**, wherein the dose of the CBD is increased to about 10 mg/kg/day to about 20 mg/kg/day.

16. A method of treating seizures in a patient with treatment-resistant Dravet syndrome, comprising administering to the patient in need thereof cannabidiol (CBD), wherein the CBD has a purity of at least 98% (w/w) CBD, and wherein the CBD is administered at a dose of 5 mg/kg/day, and then the dose is increased by 2 to 5 mg/kg increments.

17. The method of claim **16**, wherein the administering reduces total convulsive seizure frequency.

18. The method of claim **16**, wherein the dose of the CBD is increased to about 10 mg/kg/day to about 25 mg/kg/day.

19. The method of claim **16**, wherein the dose of the CBD is increased to about 15 mg/kg/day to about 25 mg/kg/day.

20. The method of claim **16**, wherein the dose of the CBD is increased to about 25 mg/kg/day.

21. The method of claim **16**, wherein the dose of the CBD is increased to about 10 mg/kg/day.

22. The method of claim **16**, wherein the dose of the CBD is increased to about 12 mg/kg/day.

23. The method of claim **16**, wherein the dose of the CBD is increased to about 14 mg/kg/day.

24. The method of claim **16**, wherein the dose of the CBD is increased to about 15 mg/kg/day.

25. The method of claim **16**, wherein the dose of the CBD is increased to about 18 mg/kg/day.

26. The method of claim **16**, wherein the dose of the CBD is increased to about 20 mg/kg/day.

27. The method of claim **16**, further comprising administering clobazam to the patient.

28. The method of claim **16**, wherein the dose of the CBD is increased to about 10 mg/kg/day to about 20 mg/kg/day.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 10,603,288 B2
APPLICATION NO. : 15/948412
DATED : March 31, 2020
INVENTOR(S) : Geoffrey Guy et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

Item (56) References Cited, Other Publications, Page 3, First Column:
"Chiu et al., "The Influence of Cannabidiol and A9-Tetrahydrocan-nabino on Cobalt Epilepsy in Rats," Epilepsia., 1979, 20:365-375."

Should read:
-- Chiu et al., "The Influence of Cannabidiol and A9-Tetrahydrocan-nabinol on Cobalt Epilepsy in Rats," Epilepsia., 1979, 20:365-375. --

Item (56) References Cited, Other Publications, Page 4, First Column:
"EPO Opposition, Expert Statement of Vincenzo Di Marco in European Appln. No. EP10734541.5, dated Sep. 9, 2016, 10 pages."

Should read:
-- EPO Opposition, Expert Statement of Vincenzo Di Marzo in European Appln. No. EP10734541.5, dated Sep. 9, 2016, 10 pages. --

Item (56) References Cited, Other Publications, Page 4, Second Column:
"GB Combined Search and Examination Report in GB Appln. No. GB1514079.l, dated May 4, 2016, 2 pages."

Should read:
-- GB Combined Search and Examination Report in GB Appln. No. GB1514079.l, dated May 4, 2016, 9 pages. --

Item (56) References Cited, Other Publications, Page 6, First Column:
"Marna et al., "Obstructive Sleep Apnea in a Clinical Series of Adult..."

Signed and Sealed this
Eleventh Day of August, 2020

Andrei Iancu
Director of the United States Patent and Trademark Office

Should read:
-- Manni et al., Obstructive Sleep Apnea in a Clinical Series of Adult... --

Item (56) References Cited, Other Publications, Page 8, Second Column:
"U.S. Appl. No. 15/449,042, filed Mar. 3, 2017, Geoffrey Guy."

Should read:
-- U.S. Appl. No. 15/449,402, filed Mar. 3, 2017, Geoffrey Guy. --