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

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present disclosure relates to the use of cannabidiol (CBD) for the treatment of Tuberous Sclerosis Complex (TSC). In particular the TSC is treatment resistant and is characterised by generalised seizures or focal seizures with impairment. The disclosure further relates to the use of CBD in combination with one or more anti-epileptic drugs (AEDs).

22 Claims, 1 Drawing Sheet

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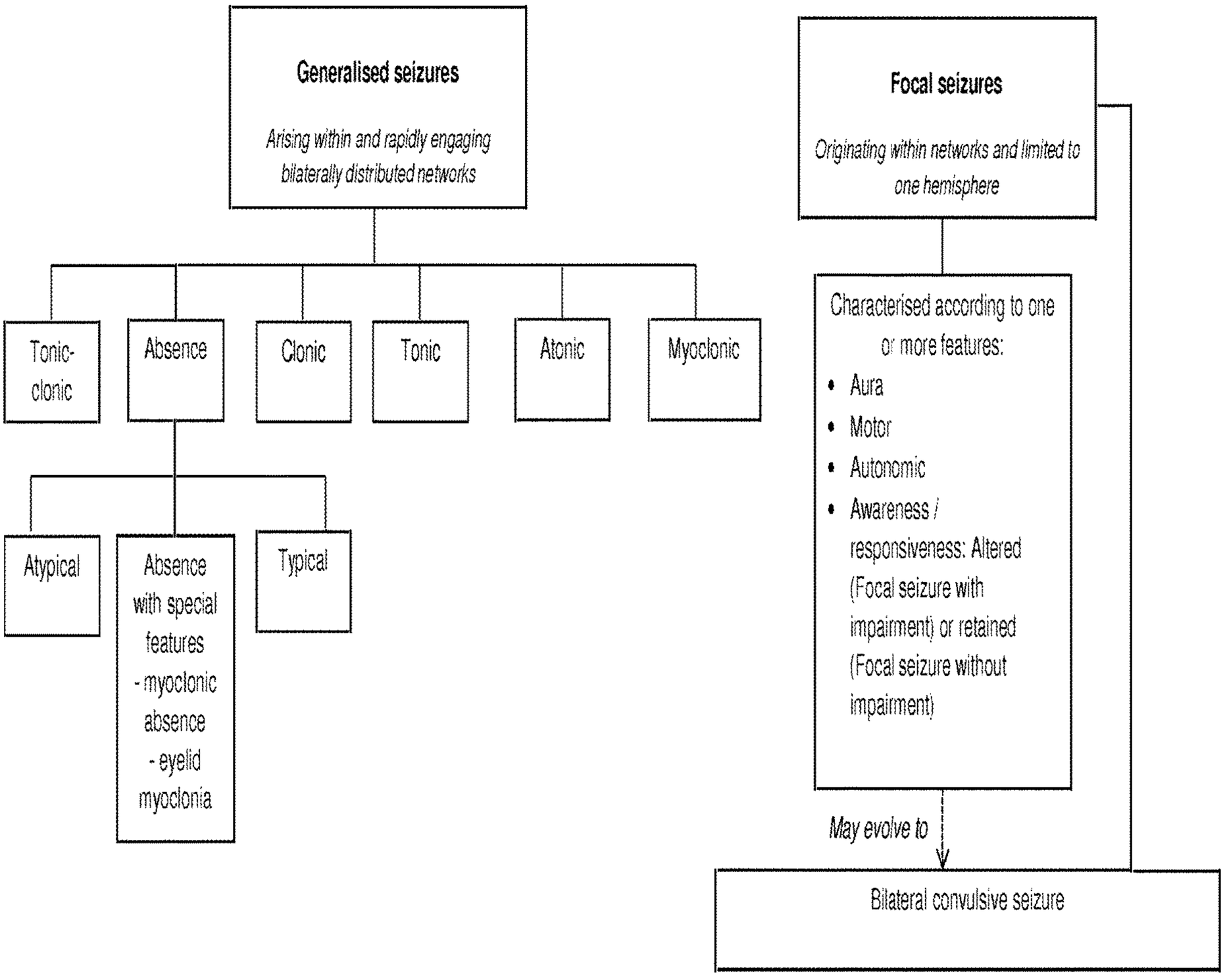


USE OF CANNABIDIOL IN THE TREATMENT OF EPILEPSY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 14/881,954, filed Oct. 13, 2015, now U.S. Pat. No. 10,918,608, which claims priority under 35 U.S.C. § 119 to United Kingdom Application No. 1418170.5, filed Oct. 14, 2014. The contents of each of the aforementioned applications are incorporated herein by reference in their entirety.

The present invention relates to the use of cannabidiol (CBD) for the treatment of Tuberous Sclerosis Complex (TSC). In particular the TSC is treatment resistant and is characterised by generalised seizures or focal seizures with impairment.

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 the cannabinoid tetrahydrocannabinol (THC) has been substantially removed, to a level of not more than 0.15% (w/w) and the propyl analogue of CBD, cannabidivarin, (CBDV) is present in amounts of up to 1%. Alternatively, the CBD may be a synthetically produced CBD.

In use the CBD is given 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. It may also be used as the sole medication, i.e. as a monotherapy.

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 intractable or "treatment-resistant epilepsy" (TRE).

Intractable or 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.

The main symptom of epilepsy is repeated seizures. In order to determine the type of epilepsy or the epileptic syndrome that a patient is suffering from an investigation into the type of seizures that the patient is experiencing is undertaken. Clinical observations and electroencephalography (EEG) tests are conducted and the type(s) of seizures are classified according to the ILEA classification described below and in FIG. **1**.

The International classification of seizure types proposed by the ILAE was adopted in 1981 and a revised proposal was published by the ILAE in 2010 and has not yet superseded the 1981 classification. FIG. **1** is adapted from the 2010 proposal for revised terminology and includes the proposed changes to replace the terminology of partial with focal. In addition the term "simple partial seizure" has been replaced by the term "focal seizure where awareness/responsiveness is not impaired" and the term "complex partial seizure" has been replaced by the term "focal seizure where awareness/consciousness is impaired".

From FIG. **1** it can be seen that Generalised seizures, where the seizure arises within and rapidly engages bilaterally distributed networks, can be split into six subtypes: Tonic-Clonic (grand mal) seizures; Absence (petit mal) Seizures; Clonic Seizures; Tonic Seizures; Atonic Seizures and Myoclonic Seizures.

Focal (partial) seizures where the seizure originates within networks limited to only one hemisphere, are also split into sub-categories. Here the seizure is characterized according to one or more features of the seizure, including aura, motor, autonomic and awareness/responsiveness. Where a seizure begins as a localized seizure and rapidly evolves to be distributed within bilateral networks this seizure is known as a bilateral convulsive seizure, which is the proposed terminology to replace Secondary Generalized Seizures (generalized seizures that have evolved from focal seizures and are no longer remain localized).

Focal seizures where the subject's awareness/responsiveness is altered are referred to as focal seizures with impairment and focal seizures where the awareness or responsiveness of the subject is not impaired are referred to as focal seizures without impairment.

Whilst focal seizures with impairment are a type of seizure commonly found to occur in the epileptic syndrome Tuberous Sclerosis Complex (TSC) these patients experience a range of different seizure types. TSC is a genetic disorder that causes mainly benign tumours to develop in certain parts of the body. When tumours develop in the brain these often cause seizures, which are often localized in one area of the brain where the tumour is.

Epilepsy is a very common feature of TSC however many patients suffering from seizures associated with TSC are unable to obtain control of their seizures using existing AED. Alternative treatments such as surgery to remove the tumours in the brain or vagus nerve stimulation may be helpful.

Epileptic syndromes such as TSC often present with many different types of seizure. Identifying the types of seizure that a patient is suffering from is important as many of the standard AED's are targeted to treat a given seizure type these can be both generalised and partial seizure types.

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

TABLE 1

Examples of narrow spectrum AED

Narrow-spectrum AED	Mechanism	Indication
Phenytoin	Sodium channel	Complex partial Tonic-clonic
Phenobarbital	GABA/ Calcium channel	Partial seizures Tonic-clonic
Carbamazepine	Sodium channel	Partial seizures Tonic-clonic Mixed seizures
Oxcarbazepine	Sodium channel	Partial seizures Tonic-clonic Mixed seizures
Gabapentin	Calcium channel	Partial seizures Mixed seizures
Pregabalin	Calcium channel	Adjunct therapy for partial seizures with or without secondary generalisation
Lacosamide	Sodium channel	Adjunct therapy for partial seizures
Vigabatrin	GABA	Secondarily generalized tonic-clonic seizures Partial seizures Infantile spasms due to West syndrome

TABLE 2

Examples of broad spectrum AED

Broad-spectrum AED	Mechanism	Indication
Valproic acid	GABA/ Sodium channel	First-line treatment for tonic-clonic seizures, absence seizures and myoclonic seizures Second-line treatment for partial seizures and infantile spasms. Intravenous use in status epilepticus
Lamotrigine	Sodium channel	Partial seizures Tonic-clonic Seizures associated with Lennox-Gastaut syndrome
Topiramate	GABA/ Sodium channel	Seizures associated with Lennox-Gastaut syndrome
Zonisamide	GABA/ Calcium/ Sodium channel	Adjunctive therapy in adults with partial-onset seizures Infantile spasm Mixed seizure Lennox-Gastaut syndrome Myoclonic Generalised tonic-clonic seizure
Levetiracetam	Calcium channel	Partial seizures Adjunctive therapy for partial, myoclonic and tonic-clonic seizures
Clonazepam	GABA	Typical and atypical absences Infantile myoclonic Myoclonic seizures Akinetic seizures

TABLE 2-continued

Examples of broad spectrum AED

Broad-spectrum AED	Mechanism	Indication
Rufinamide	Sodium channel	Adjunctive treatment of partial seizures associated with Lennox-Gastaut syndrome

TABLE 3

Examples of AED used specifically in childhood epilepsy

AED	Mechanism	Indication
Clobazam	GABA	Adjunctive therapy in complex partial seizures Status epilepticus Myoclonic Myoclonic-absent Simple partial Complex partial Absence seizures Lennox-Gastaut syndrome
Stiripentol	GABA	Severe myoclonic epilepsy in infancy (Dravet syndrome)

Over the past forty years there have been a number of animal and human studies on the use of the non-psychoactive cannabinoid cannabidiol (CBD) to treat seizures.

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).

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) and Consroe et al., (1982) determined that CBD was able to prevent seizures in mice after administration of pro-convulsant drugs or an electric current.

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).

All of the studies described above focused on the treating subjects suffering from generalised epilepsy and did not look at the treatment of specific seizure sub-types.

More recently, WO 2011/001169 describes the use of CBD in the treatment of focal seizures, WO 2012/093255 describes the use of CBD in combination with standard anti-epileptic drugs in the treatment of epilepsy and WO 2013/045891 describes a composition comprising CBD and CBDV for use in the treatment of epilepsy.

In November 2013 the company GW Pharmaceuticals made a press release to state that they were intending to treat Dravet Syndrome with CBD as it had received orphan drug designation. The company made a further press release in February 2014 that that they were intending to treat Lennox-Gastaut Syndrome with CBD as it had also received orphan drug designation.

Again the rationale was to treat a disease as opposed to the type of seizure that the subject experienced.

It has additionally been suggested that cannabis which is enriched in CBD may be efficacious in the treatment of epilepsy. A case study of a child with Lennox-Gastaut syndrome showed improvement in seizure frequency after treatment with CBD in an oily solution was reported in 2005 (Pelliccia et al. 2005).

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 for many of the cases. 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), at a potentially psychoactive dose of 0.8 mg/kg/day, is a concern.

In addition a paper published in June 2014 describes the use of a high-CBD strain to treat a patient with Dravet Syndrome; the patient's seizure frequency was stated to be reduced by the treatment (Maa et al. 2014).

A document published after the priority application was filed discloses the use of CBD in the treatment of refractory epilepsy in the treatment of Tuberous Sclerosis Complex in patients having focal onset seizures (Geffrey et al., 2014).

Whilst the potential of cannabis and the cannabinoids, including CBD, to treat epilepsy has been rekindled, to date there has been little in the way of real data to support its efficacy in patients.

The applicant has found that CBD shows significant efficacy in half of the patients with TSC as these benefitted from at least a fifty percent reduction in the total number of seizures. Furthermore, the fact that in this group of responders the average reduction in the total number of seizures was so pronounced (an 80% reduction) is very surprising.

It is additionally worth noting that the patients being treated were treatment resistant to existing AED and so consequently these figures are even the more remarkable.

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 Tuberous Sclerosis Complex (TSC).

Preferably the TSC is treatment resistant.

More preferably the TSC is characterized by generalised seizures or focal seizures with impairment. The generalised seizures may include one or more of seizure sub-types; tonic; atonic; tonic-clonic; and absence seizures.

Seizures that are associated with TSC include: focal seizures with impairment; tonic; atonic; tonic-clonic; and absence seizures.

Patients with TSC may also encounter aspects of cognitive impairment of: alertness, comprehension, maintained eye contact, engagement, responsiveness and behavioural problems.

In one embodiment the CBD is used in combination with one or more concomitant anti-epileptic drugs (AED).

In a further embodiment the CBD is present as a highly purified extract of cannabis which comprises at least 95% (w/w) CBD, more preferably 98% (w/w) CBD. Preferably the extract comprises less than 0.15% THC. More preferably the extract further comprises up to 1% CBDV.

In a further embodiment of the invention the one or more AED is selected from the group consisting of: clobazam; diazepam; lacosamide; lamotrigine; levetiracetam; lorazepam; nordiazepam; n-desmethylclobazam; phenytoin; valproic acid; zonisamide.

Preferably the number of different anti-epileptic drugs that are used in combination with the CBD is reduced. Alternatively the dose of the one or more anti-epileptic drugs that are used in combination with the CBD is reduced.

Preferably the dose of CBD is greater than 5 mg/kg/day.

In accordance with a second aspect of the present invention there is provided a method of treating Tuberous Sclerosis Complex (TSC) comprising administering cannabidiol (CBD) to a subject.

In accordance with a third aspect of the present invention there is provided a composition for use in the treatment of atonic seizures characterised by atonic seizures comprising cannabidiol (CBD), a solvent, a co-solvent, a sweetener, and a flavouring.

Preferably the solvent is sesame oil, the co-solvent is ethanol, the sweetener is sucralose, the flavouring is strawberry flavour and the CBD is present at a concentration of between 25/mg/ml and 100 mg/ml.

More preferably the composition comprises cannabidiol (CBD) at a concentration of between 25 to 100 mg/ml, ethanol at a concentration of 79 mg/ml, sucralose at a concentration of 0.5 mg/ml, strawberry flavouring at a concentration of 0.2 mg/ml and sesame q.s. to 1.0 ml.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a schematic of the ILEA classification of types of seizures.

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.

TABLE 4

Cannabinoids and their abbreviations

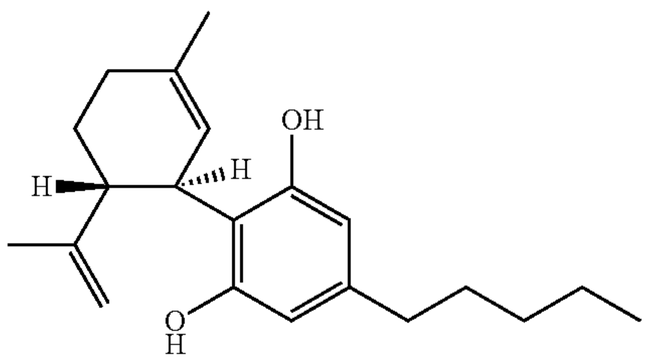
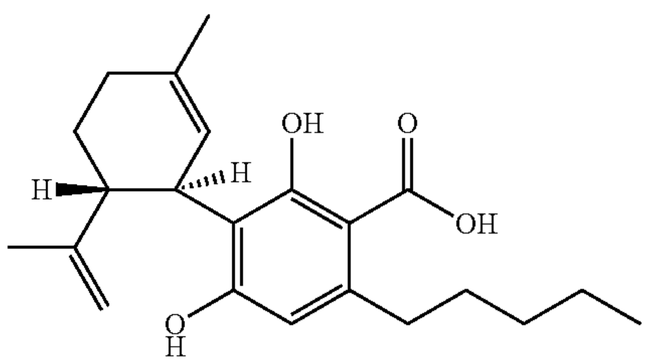
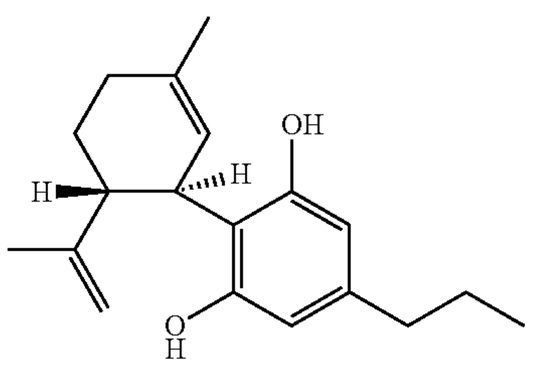
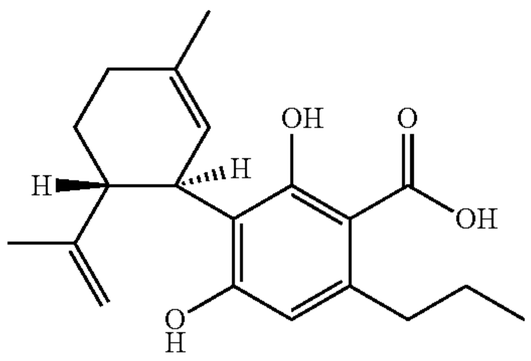
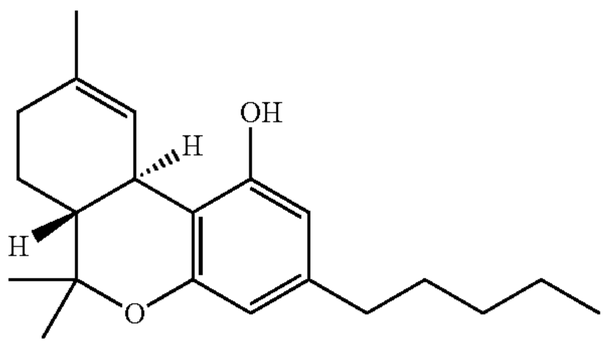
CBD	Cannabidiol	
CBDA	Cannabidiolic acid	
CBDV	Cannabidivarin	

TABLE 4-continued

Cannabinoids and their abbreviations

CBDVA	Cannabidivarinic acid	
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 95% (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) or "intractable epilepsy" 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: Tuberous Sclerosis Complex; 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.

"Focal Seizures" are defined as seizures which originate within networks limited to only one hemisphere. What happens during the seizure depends on where in the brain the seizure happens and what that part of the brain normally does.

"Focal seizure where awareness/consciousness are impaired" has replaced the term "complex partial seizure". These seizures usually start in a small area of the temporal lobe or frontal lobe of the brain and involve other areas of the brain within the same hemisphere that affect alertness and awareness. Most subjects experience automatisms during a focal seizure with impaired consciousness.

"Mixed seizures" are defined as the existence of both generalised and focal seizures in the same patient.

The terms "50% responder" and "50% reduction in seizure" are both terms used in clinical studies. In the present application the terms define the percentage of subjects that experienced a greater than or equal to 50% reduction in the total number of seizures during treatment with CBD in comparison to the number experienced during the baseline period before the CBD was administered.

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 95% CBD w/w, typically greater than 98% w/w.

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 5 below.

TABLE 5

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

TABLE 5-continued

CBD Specification		
Test	Test Method	Limits
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 %
Other Cannabinoids:	HPLC-UV	NMT 0.15% w/w
CBDA		NMT 1.0% w/w
CBDV		NMT 0.15% w/w
Δ^9 THC		NMT 0.5% w/w
CBD-C4		
Residual Solvents:	GC	NMT 0.5% w/w
Alkane		NMT 0.5% w/w
Ethanol		
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 other cannabinoids which may occur in the extract are: 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 volts) 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.

Production of the Drug Product

The drug product is presented as an oral solution. The oral solution presentation contains 25 mg/ml or 100 mg/ml CBD, with the excipients sesame oil, ethanol, sucralose and flavouring. Two product strengths are available to allow dose titration across a wide dose range.

The 25 mg/ml solution is appropriate at lower doses and the 100 mg/ml solution at higher doses.

The drug product formulation is as described in Table 6 below:

TABLE 6

Drug Product specification			
Component	Qualitative Composition	Function	Reference to Quality Standard
Cannabidiol (CBD)	25 mg/ml or 100 mg/ml	Active	In-house
Anhydrous ethanol	79.0 mg/ml*	Excipient	Ph.Eur.
Sucralose	0.5 mg/ml	Sweetener	In-house
Strawberry flavouring	0.2 mg/ml	Flavouring	In-house
Sesame oil	q.s to 1.0 ml	Excipient	Ph.Eur.

The drug substance, CBD is insoluble in water. Sesame oil was selected as an excipient to solubilize the drug substance.

A sweetener and fruit flavouring are required to improve palatability of the sesame oil solution.

Ethanol was required to solubilize the sweetener and the flavouring.

The composition can be substantially equivalent, by which is meant the functional ingredients can vary from the qualitative composition specified in Table 6 by an amount of up to 10%.

Example 1 below describes the use of a highly purified *cannabis* extract comprising cannabidiol (CBD) in an expanded access treatment program in children with TRE.

Example 1: Efficacy of Cannabidiol Reducing Seizures in Children and Young Adults with Tuberous Sclerosis Complex

Materials and Methods

Of 137 children and young adults with severe, childhood onset treatment-resistant epilepsy (TRE), twelve suffered from Tuberous Sclerosis Complex (TSC). These subjects 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 of these patients diagnosed with TSC presented with one or more types of seizure including tonic, tonic-clonic, atonic, absence, focal seizures with impairment and focal seizures which evolve to secondary generalised seizures.

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

All patients were taking at least two concomitant anti-epileptic drugs. These included clobazam; diazepam; lacosamide; lamotrigine; levetiracetam; lorazepam; nordiazepam; n-desmethylclobazam; phenytoin; valproic acid; zonisamide. The average number of concomitant antiepileptic drugs being taken was 2.7. The majority took either clobazam and/or valproic acid.

Results

There were 12 children and young adult patients who received at least 3 months of treatment all of whom suffered from treatment-resistant epilepsy with a diagnosis of Tuberous Sclerosis Complex (TSC).

A summary of the percentage change from baseline in total number of seizures after 12 weeks treatment are summarized in Table 7 below.

TABLE 7

Changes in baseline for total number of seizures

Subject number	Change in baseline (%)	>50% reduction in seizures
1	108.0	No
2	−39.2	No
3	−63.2	Yes
4	−93.7	Yes
5	−15.0	No
6	−71.0	Yes
7	−33.5	No
8	−80.2	Yes
9	0.4	No
10	−100.0	Yes
11	−9.8	No
12	−74.4	Yes

Table 7 shows that after 3 months of therapy, there was a decrease in total seizure frequency with ten out of 12 of the TSC patients. Furthermore six of the 12 experienced a greater than 50% reduction in total seizures over the 12 weeks of treatment. The average reduction in the total number of seizures in these patients was 80.4%.

These data infer that the CBD is effective at treating this intractable and difficult to treat patient group and was surprisingly able to reduce the total seizure frequency in over 80% of the patients treated.

Table 8 summarises the reduction in the number of focal seizures and focal seizure sub-types, and Table 9 summarises the reduction in the number of generalised seizure sub-types.

TABLE 8

Summary of 50% responders after 12 weeks of treatment for focal seizures

	Total focal seizures (n = 14)	Focal seizures with impairment (n = 10)	Focal seizures evolving to secondary generalisation (n = 2)
>50% reduction in seizures	45%	55%	50%
<50% reduction in seizures	55%	45%	50%

TABLE 9

Summary of 50% responders after 12 weeks of treatment for generalised seizures

	Tonic seizures (n = 5)	Atonic seizures (n = 3)	Tonic-clonic seizures (n = 2)	Absence seizures (n = 2)
>50% reduction in seizures	75%	100%	100%	100%
<50% reduction in seizures	25%	0%	0%	0%

As can be seen from Tables 8 and 9 above the treatment with CBD was able to dramatically reduce the incidence of the generalised seizure types tonic, atonic, tonic-clonic and absence seizures. In addition the CBD treatment also markedly reduced the number of focal seizures with impairment.

From the 12 patients with TSC that were treated with CBD, ten of these patients experienced seizures which were focal with impairment. These data therefore suggest that treatment with CBD is likely to be a significant treatment option for TSC patients.

CONCLUSIONS

These data indicate that CBD significantly reduces the number of seizures in a high proportion of patients that do not respond well to existing AED.

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 half of the patients benefitted from at least a fifty percent reduction in the total number of seizures that they suffered from was remarkable. Furthermore the fact that in this group of responders the average reduction in the number of seizures was 80% is very surprising.

It was also demonstrated that treatment with CBD was able to virtually eliminate the generalised seizures that a TSC patient suffers from. Again this is very surprising particularly in this group of patients that were resistant to existing medications.

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The invention claimed is:

1. A method of treating seizures in a patient suffering from Tuberous Sclerosis Complex (TSC) comprising administering cannabidiol (CBD) to the patient, wherein the CBD has a purity of at least 98% (w/w) CBD, and wherein the CBD is administered at a dose ranging from 5 mg/kg/day to 25 mg/kg/day.

2. The method according to claim **1**, wherein the TSC is treatment resistant.

3. The method according to claim **1**, wherein the TSC is characterized by generalized seizures or focal seizures with impairment.

4. The method according to claim **3**, wherein the generalized seizures include one or more seizure sub-types selected from the group consisting of tonic; atonic; tonic-clonic; and absence seizures.

5. The method according to claim **1**, wherein the CBD is administered in combination with a therapeutic dose of one or more concomitant anti-epileptic drugs (AED).

6. The method according to claim **1**, wherein the CBD is present as a synthetic compound.

7. The method according to claim **1**, wherein the CBD is administered as a highly purified extract.

8. The method according to claim **5**, wherein the one or more AED is selected from the group consisting of: clobazam; diazepam; lacosamide; lamotrigine; levetiracetam; lorazepam; nordiazepam; n-desmethylclobazam; phenytoin; valproic acid; and zonisamide.

9. The method according to claim **5**, wherein the number of different AED that are administered in combination with the CBD to the subject in need thereof is reduced relative to the number of AED administered prior to treatment with CBD.

10. The method according to claim **5**, wherein the dose of the one or more AED that are used in combination with the CBD is reduced relative to the dose of AED administered prior to treatment with CBD.

11. The method according to claim **5**, wherein the AED is clobazam.

12. The method according to claim **5**, wherein the AED is valproic acid.

13. The method according to claim **1**, wherein the dose of CBD is 20 mg/kg/day.

14. The method according to claim **1**, wherein the dose of CBD is 25 mg/kg/day.

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

16. The method according to claim **1**, wherein the dose of CBD is 15 mg/kg/day.

17. A method of treating seizures in a patient suffering from Tuberous Sclerosis Complex (TSC) comprising administering cannabidiol (CBD) to the patient, wherein the CBD has a purity of at least 98% (w/w) CBD, and wherein the CBD is administered at 25 mg/kg/day.

18. The method of claim **1**, wherein the CBD is administered as a highly purified extract in an oral solution comprising ethanol, sucralose, strawberry flavouring, and sesame oil.

19. The method of claim **18**, wherein the extract comprises 100 (±10%) mg/mL CBD, 79.0 (±10%) mg/mL ethanol, 0.5 (±10%) mg/mL sucralose, and 0.2 (±10%) mg/mL strawberry flavouring.

20. The method according to claim **17**, wherein the CBD is present as a synthetic compound.

21. The method of claim **17**, wherein the CBD is administered as a highly purified extract in an oral solution comprising ethanol, sucralose, strawberry flavouring, and sesame oil.

22. The method of claim **21**, wherein the extract comprises 100 (±10%) mg/mL CBD, 79.0 (±10%) mg/mL ethanol, 0.5 (±10%) mg/mL sucralose, and 0.2 (±10%) mg/mL strawberry flavouring.

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