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(54) Title: USE OF CANNABIDIOL IN THE TREATMENT OF EPILEPSY

(57) Abstract: The present disclosurerelates to the use of cannabidiol (CBD) in the treatment of absence seizures. In particular, the disclosure relates to the use of CBD for reducing absence seizures in patients suffering withetiologies that include: Lennox-Gastaut Syndrome; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; CDKL5; Dup15q;, Jeavons syndrome; Myoclonic Absence Epilepsy;Neuronal ceroid lipofuscinoses(NCL) and brain abnormalities. The disclosure further relates to the use of CBD in combination with one or more anti-epileptic drugs (AEDs).

USE OF CANNABIDIOL IN THE TREATMENT OF EPILEPSY

FIELD OF THE INVENTION

[0001] The present invention relates to the use of cannabidiol (CBD) in the treatment of absence seizures. In one embodiment the patients suffering from absence seizures are children and young adults. CBD appears particularly effective in reducing absence seizures in patients suffering with etiologies that include: Lennox-Gastaut Syndrome; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; CDKL5; Dup15q; , Jeavons syndrome; Myoclonic Absence Epilepsy; Neuronal ceroid lipofuscinoses (NCL) and brain abnormalities in comparison to other seizure types.

[0002] Significantly CBD proved very effective in treating a sub-type of absence seizures, namely myoclonic absence seizures. The etiologies of patients which suffer from myoclonic absence seizures include Doose Syndrome, Jeavons syndrome and Myoclonic Absence Epilepsy syndrome.

[0003] In these patients treatment with CBD reduced the occurrence of absence seizures or myoclonic absence seizures by greater than 50% in a large proportion of patients, 64% and 75% respectively. This was surprising given that the proportion of patients benefitting from a greater than 50% reduction in total seizures was significantly less, (46%), in all subjects treated.

[0004] 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.

[0005] In use the CBD may be used concomitantly with one or more other anti-epileptic drugs (AED). When used in combination with another AED the CBD may be formulated for administration separately, sequentially or simultaneously with the 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

[0006] 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).

[0007] 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).

[0008] 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.

[0009] 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.

[0010] 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.

[0011] 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 ILAE classification described below and in Figure 1.

[0012] 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. Figure 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".

[0013] From Figure 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.

[0014] 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 Generalised Seizures (generalized seizures that have evolved from focal seizures and are no longer remain localized).

[0015] Absence seizures can occur as Typical absence seizures; Atypical absence seizures or Absence seizures with special features such as Myoclonic absence and Eyelid myoclonia.

[0016] Typical absence seizures are generalized seizures with a sudden onset and offset of altered awareness. The altered awareness can vary in severity dependent on the specific syndrome that the patient is suffering from. Clonic movements of the eyelids, head, eyebrows, chin perioral or other facial parts can occur, whereas myoclonus of limbs only occurs rarely. In addition, absence status epilepticus can also occur.

[0017] Atypical absence seizures have a less sudden onset and offset of loss of awareness than occurs in typical absence seizures. They are associates with other features such as loss of muscle tone of the head, trunk or limbs and subtle myoclonic jerks. A loss of awareness is usually minimal.

[0018] Myoclonic absence seizures present with bilateral rhythmic myoclonic jerks of the shoulders and arms. There is tonic abduction which results in progressive lifting of the arms during the seizure. Seizures last between 10 and 60 seconds and there may be a complete loss of awareness.

[0019] Eyelid myoclonia are absence seizures which are accompanied by brief repetitive myoclonic jerks of the eyelids with simultaneous upward deviation of the eyeballs and extension of the head. Seizures are typically brief and multiple seizures can occur on a daily basis. Awareness is mostly retained.

[0020] Absence seizures may occur in epilepsy syndromes including: Lennox-Gastaut Syndrome; Myoclonic Absence Epilepsy; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; CDKL5; Dup15q; Jeavons Syndrome; Myoclonic Absence Epilepsy; Neuronal ceroid lipofuscinoses (NCL) and brain abnormalities.

[0021] Epileptic syndromes often present with many different types of seizure and identifying the types of seizure that a patient is suffering from is important as many of the

standard AED's are targeted to treat or are only effective against a given seizure type / sub-type.

[0022] The first line treatment for absence seizures usually comprises a broad spectrum AED, such as sodium valproate, lamotrigine or ethosuximide. A combination of these medicaments may be required in order to treat absence seizures.

[0023] Common AED defined by their mechanisms of action are described in the following tables:

[0024] **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

[0025] 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
Ethosuximide	Calcium channel	Absence seizures
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
Rufinamide	Sodium channel	Adjunctive treatment of partial seizures associated with Lennox-Gastaut syndrome

[0026] 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)

[0027] From these tables it can be seen that the three AED that are used as first line treatments for absence seizures, namely: sodium valproate, lamotrigine or ethosuximide are GABA/sodium channel, sodium channel and calcium channel drugs respectively.

[0028] It can also be seen from these tables that other AED are approved for use in absence seizures, these include clonazepam and clobazam, both of which work by a GABA mechanism.

[0029] 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.

[0030] 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).

[0031] 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).

[0032] 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).

[0033] 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, possibly 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).

[0034] 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 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.

[0035] 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 and as such there is a need to determine whether CBD is in fact efficacious.

[0036] 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.

[0037] To date there have been no controlled trials of CBD in children and young adults with intractable epilepsy.

BRIEF SUMMARY OF THE DISCLOSURE

[0038] In accordance with a first aspect of the present invention there is provided cannabidiol (CBD) for use in the treatment of epilepsy, wherein the epilepsy is characterised by absence seizures.

[0039] In one embodiment the epilepsy is a childhood epilepsy.

[0040] In one embodiment the absence seizures are myoclonic absence seizures.

[0041] Surprisingly, the CBD has been shown to be particularly effective in subjects with epilepsy which is treatment-resistant.

[0042] In a further embodiment the CBD is for use in combination with one or more concomitant anti-epileptic drugs (AED).

[0043] Preferably the absence seizures to be treated are in patients diagnosed with: Lennox-Gastaut Syndrome; Myoclonic Absence Epilepsy; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; Jeavons Syndrome; CDKL5; Dup15q; Neuronal ceroid lipofuscinoses (NCL) and brain abnormalities.

[0044] Most preferably the treatment-resistant epilepsy is one of: Lennox-Gastaut Syndrome; Dravet Syndrome and Myoclonic Absence Epilepsy.

[0045] In a further embodiment the CBD is present as a highly purified extract of cannabis which comprises at least 98% (w/w) CBD. Preferably the extract comprises less than 0.15% THC. More preferably the extract further comprises up to 1% CBDV.

[0046] In an alternative embodiment the CBD is present as a synthetic compound.

[0047] In a further embodiment of the invention the one or more AED is selected from the group consisting of: clobazam, clonazepam, clorazepate, desmethylclobazam, diazepam, ethosuximide, felbamate, gabapentin, ketogenic diet, lacosamide, lamotrigine, levetiracetam, lorazepam, midazolam, N-desmethylclobazam, nordiazepam, phenytoin, stiripentol, topiramate, trazodone, vagus nerve stimulation, valproic acid, vigabatrin, and zonisamide.

[0048] Preferably the one or more AED is selected from the group consisting of sodium valproate; lamotrigine; ethosuximide; clobazam and clonazepam.

[0049] Preferably the number of different anti-epileptic drugs that are used in combination with the CBD is reduced. Alternatively the dose of anti-epileptic drugs that are used in combination with the CBD is reduced.

[0050] There are many side effects associated with the commonly used AED which include dizziness, blurred vision, nausea, respiratory system depression, tiredness, headaches, and other motor side effects on the central nervous system. These side effects are particularly common as higher doses or combinations of numerous AED are used. As such there is a need for an alternative medication that is able to reduce the numbers of seizures whilst at the same time exhibiting a safe side effect profile.

[0051] Preferably the dose of CBD is greater than 5 mg/kg/day. Thus for a 15 kg patient a dose of greater than 75mg of CBD per day would be provided. Doses greater than 5mg/kg/day

such as greater than 10/mg/kg/day, greater than 15 mg/kg/day, greater than 20mg/kg/day and greater than 25 mg/kg/day are also envisaged to be effective.

[0052] Preferably the epilepsy is childhood epilepsy.

[0053] In accordance with a second aspect of the present invention there is provided a method of treating epilepsy comprising administering cannabidiol (CBD) to a subject, wherein the epilepsy is characterised by absence seizures.

[0054] Preferably the subject is a human, typically a patient that is suffering from epilepsy characterised by absence seizures.

[0055] In accordance with a third aspect of the present invention there is provided a composition for use in the treatment of epilepsy characterised by absence seizures comprising cannabidiol (CBD), a solvent, a co-solvent, a sweetener, and a flavouring.

[0056] 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, namely 50mg/ml and 75 mg/ml.

[0057] 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 oil q.s. to 1.0ml.

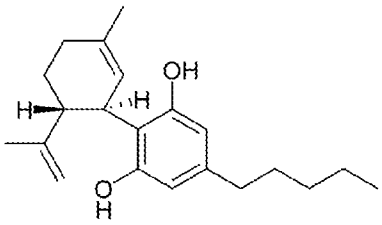
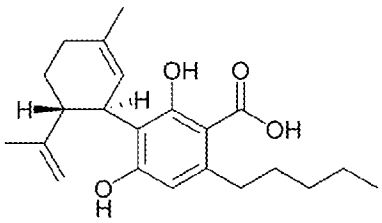
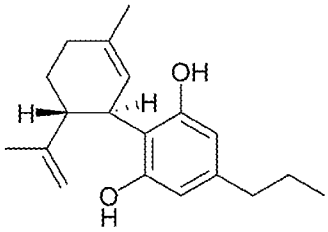
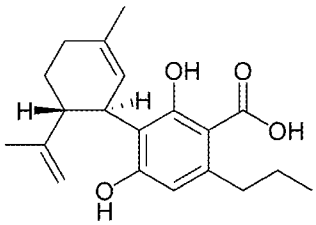
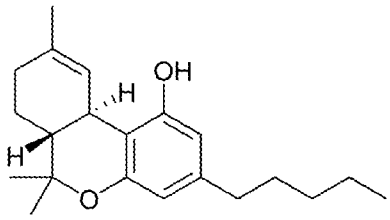
[0058] It is envisaged that the composition be administered as an oral liquid solution. Other modes of administration including solids, semi-solids, gels, sprays, aerosols, inhalers, vaporisers, enemas and suppositories are alternative administration forms. Such medicaments could be administered via the oral, buccal, sublingual, respiratory, nasal and distal rectum route.

DEFINITIONS

[0059] Definitions of some of the terms used to describe the invention are detailed below:

[0060] 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	
CBDVA	Cannabidivarinic acid	
THC	Tetrahydrocannabinol	

[0061] 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).

[0062] "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.

[0063] "Highly purified cannabinoid extracts" 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 substantially removed, such that the highly purified cannabinoid is greater than or equal to 98% (w/w) pure.

[0064] "Synthetic cannabinoids" are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.

[0065] 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.

[0066] "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.

[0067] "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.

[0068] "Absence Seizures" are defined as a generalised type of epileptic seizure which causes a loss of awareness often accompanied by myoclonic jerks.

[0069] "Myoclonic Absence Seizures" are defined as a sub-type of absence seizures which present with bilateral myoclonic jerks of the arms and shoulders.

[0070] "Mixed seizures" are defined as the existence of both generalised and focal seizures in the same patient.

[0071] 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 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

[0072] 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 the Examples below.

[0073] 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.

[0074] 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).

[0075] 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.

[0076] 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
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: - CBDA	HPLC-UV	

Test	Test Method	Limits
- CBDV - Δ^9 THC - CBD-C4		NMT 0.15% w/w NMT 1.0% w/w NMT 0.15% w/w NMT 0.5% w/w
Residual Solvents: - Alkane - Ethanol	GC	 NMT 0.5% w/w NMT 0.5% w/w
Residual Water	Karl Fischer	NMT 1.0% w/w

NMT- Not more than

[0077] 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.

[0078] 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

[0079] 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

[0080] 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 1mm screen. The milled BRM was stored in a freezer for up to 3 months prior to extraction.

[0081] 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 105ºC; the BRM took 96.25 minutes to reach 105 ºC. Held at 105ºC for 15 Minutes. Oven then set to 150ºC.; the BRM took 75.7 minutes to reach 150ºC; BRM held at 150ºC for 130 Minutes. Total time in the oven was 380 Minutes, including 45 minutes cooling and 15 Minutes venting.

[0082] Extraction No 1 was performed using liquid CO_2 at 60 bar / 10°C to produce botanical drug substance (BDS).

[0083] 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, which was then used for crystallisation to produce the test material..

Production of the Drug Substance

[0084] 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

[0085] Intermediate botanical extract (12kg) 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.

[0086] The mixture was manually agitated to break up any lumps and the sealed container then placed in a freezer for approximately 48 hours.

[0087] 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 < 10mb at a temperature of 60°C until dry before submitting the drug substance for analysis.

[0088] 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

[0089] The drug product is presented as an oral solution. The oral solution presentation contains 25mg/ml or 100mg/ml CBD, with the excipients sesame oil, ethanol, sweetener and flavouring. Two product strengths are available to allow dose titration across a wide dose range.

[0090] The 25 mg/ml solution is appropriate at lower doses and the 100 mg/ml solution at higher doses.

[0091] 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.

[0092] The drug substance, CBD is insoluble in water. Sesame oil was selected as an excipient to solubilize the drug substance.

[0093] A sweetener and fruit flavouring are required to improve palatability of the sesame oil solution.

[0094] Ethanol was required to solubilize the sweetener and the flavouring.

[0095] 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%.

[0096] Example 1 below describes the use of a highly purified cannabis extract comprising cannabidiol (CBD). Cannabidiol is the most abundant non-psychoactive cannabinoid in the selected chemovar. Previous studies in animals have demonstrated that CBD has anticonvulsant efficacy in multiple species and models.

[0097] Example 1 describes data produced in an expanded access treatment program in children with TRE.

EXAMPLE 1: EFFICACY OF CANNABIDIOL REDUCING ABSENCE SEIZURES IN CHILDREN AND YOUNG ADULTS WITH INTRACTABLE EPILEPSY

Materials and Methods

[0098] Of 137 children and young adults with severe, childhood onset treatment-resistant epilepsy (TRE), forty-two suffered from epilepsy that was characterised by absence seizures. These subjects were tested with a highly purified extract of cannabidiol (CBD) obtained from a cannabis plant. All subjects presented with absence type seizures, often in addition to other generalised and / or focal seizures. The participants in the study were part of an expanded access compassionate use program for CBD.

[0099] The epileptic syndromes that these patients suffered from were as follows: Lennox-Gastaut Syndrome; Myoclonic Absence Epilepsy; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; Jeavons Syndrome; CDKL5; Dup15q; Neuronal ceroid lipofuscinoses (NCL) and brain abnormalities.

[00100] Seizure types experienced by these patients included: tonic, clonic, tonic-clonic, myoclonic, atonic, absence, myoclonic-absence, focal seizures without impairment, focal seizures with impairment and focal seizures evolving to bilateral convulsive seizures.

[00101] All patients entered a baseline period of 4 weeks when parents/caregivers kept prospective seizure diaries, noting all countable seizure types.

[00102] 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.

[00103] The daily dose was gradually increased by 2 to 5mg/kg increments until intolerance occurred or a maximum dose of 25 mg/kg/day was achieved.

[00104] 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 every 4 weeks of CBD therapy.

[00105] The patients on the study were all taking at least one concomitant AED. These included clobazam, clonazepam, clorazepate, desmethylclobazam, diazepam, ethosuximide, felbamate, gabapentin, ketogenic diet, lacosamide, lamotrigine, levetiracetam, lorazepam, midazolam, N-desmethylclobazam, nordiazepam, phenytoin, stiripentol, topiramate, trazodone, vagus nerve stimulation, valproic acid, vigabatrin, and zonisamide.

Results

[00106] Of the 42 children and young adult patients who received treatment with CBD, there were 28 patients who received treatment for at least 12 weeks of treatment all of whom suffered from absence type seizures.

[00107] A summary of the 50% responders, based on 12 weeks of treatment are summarized in Table 7 below.

Table 7. Summary of 50% responders after 12 weeks of treatment

	Absence seizures (n=28)	**Total seizures (n=137)**
> 50% reduction in seizures	64% (n=18)	46% (n=63)

< 50% reduction in seizures	36% (n=10)	54% (n=74)

[00108] Table 7 shows that after 3 months of therapy, a remarkable 64% of patients had an equal to or greater than >50% reduction in absence seizures, these data infer that the CBD is very effective at reducing this type of seizure.

Conclusions

[00109] These data indicate that CBD significantly reduces the number of absence type seizures in a high proportion of patients that do not respond well to existing AED.

[00110] 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 two thirds of the patients (64%) benefitted from at least a fifty percent reduction in the number of absence seizures that they suffered from was remarkable.

EXAMPLE 2: EFFICACY OF CANNABIDIOL REDUCING MYOCLONIC ABSENCE SEIZURES IN CHILDREN AND YOUNG ADULTS WITH INTRACTABLE EPILEPSY

Materials and Methods

[00111] Of 137 children and young adults with severe, childhood onset treatment-resistant epilepsy (TRE), ten suffered from epilepsy that was characterised by myoclonic absence seizures. These subjects were tested with a highly purified extract of cannabidiol (CBD) obtained from a cannabis plant. All subjects presented with myoclonic absence type seizures, often in addition to other generalised and / or focal seizures. The participants in the study were part of an expanded access compassionate use program for CBD.

[00112] The epileptic syndromes that these patients suffered from were as follows: Myoclonic Absence Epilepsy; Doose Syndrome; and epilepsy of unknown cause.

[00113] All patients entered a baseline period of 4 weeks when parents/caregivers kept prospective seizure diaries, noting all countable seizure types.

[00114] 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.

[00115] The daily dose was gradually increased by 2 to 5mg/kg increments until intolerance occurred or a maximum dose of 25 mg/kg/day was achieved.

[00116] 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 every 4 weeks of CBD therapy.

[00117] The patients on the study were all taking at least one concomitant AED. These included clobazam, clonazepam, clorazepate, diazepam, ethosuximide, ketogenic diet, lacosamide, lamotrigine, levetiracetam, lorazepam, midazolam, and valproic acid.

Results

[00118] Of the 10 children and young adult patients who received treatment with CBD, there were 8 patients who received treatment for at least 12 weeks of treatment all of whom suffered from myoclonic absence type seizures.

[00119] A summary of the 50% responders, based on 12 weeks of treatment are summarized in Table 8 below.

Table 8. Summary of 50% responders after 12 weeks of treatment

	Myoclonic absence seizures (n=10)	**Total seizures (n=137)**
> 50% reduction in seizures	75% (n=6)	46% (n=63)
< 50% reduction in seizures	25% (n=2)	54% (n=74)

[00120] Table 8 shows that after 3 months of therapy, a remarkable 75% of patients had an equal to or greater than >50% reduction in absence seizures, these data infer that the CBD is very effective at reducing this type of seizure.

Conclusions

[00121] These data indicate that CBD significantly reduces the number of myoclonic absence seizures in a high proportion of patients that do not respond well to existing AED.

[00122] 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 three quarters of the patients (75%) benefitted from at least a fifty percent reduction in the number of myoclonic absence seizures that they suffered from was remarkable.

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CLAIMS

1. Cannabidiol (CBD) for use in the treatment of epilepsy, wherein the epilepsy is characterised by absence seizures.

2. CBD for use according to claim 1, wherein the absence seizures are myoclonic absence seizures.

3. Cannabidiol (CBD) for use according to claim 1 or claim 2, wherein the epilepsy is treatment-resistant epilepsy (TRE).

4. CBD for use according to any of the preceding claims, wherein the CBD is for use in combination with one or more concomitant anti-epileptic drugs (AED).

5. CBD for use according to any of the preceding claims, wherein the absence seizures to be treated are in subjects diagnosed with: Lennox-Gastaut Syndrome; Myoclonic Absence Epilepsy; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; Jeavons Syndrome; CDKL5; Dup15q; Neuronal ceroid lipofuscinoses (NCL) and brain abnormalities.

6. CBD for use according to claim 5, wherein the subject is diagnosed with Lennox-Gastaut Syndrome.

7. CBD for use according to claim 5, wherein the subject is diagnosed with Dravet Syndrome.

8. CBD for use according to claim 5, wherein the subject is diagnosed with Myoclonic Absence Epilepsy.

9. CBD for use according to any of the preceding claims, wherein the CBD is present as a highly purified extract of cannabis which comprises at least 98% (w/w) CBD.

10. CBD for use according to claim 9 wherein the extract comprises less than 0.15% THC.

11. CBD for use according to claim 9 or 10 wherein the extract further comprises up to 1% CBDV.

12. CBD for use according to any of the preceding claims, where in the CBD is present as a synthetic compound.

13. CBD for use according to claim 4, wherein the one or more AED is selected from the group consisting of: clobazam, clonazepam, clorazepate, desmethylclobazam, diazepam, ethosuximide, felbamate, gabapentin, ketogenic diet, lacosamide, lamotrigine, levetiracetam, lorazepam, midazolam, N-desmethylclobazam, nordiazepam, phenytoin, stiripentol, topiramate, trazodone, vagus nerve stimulation, valproic acid, vigabatrin, and zonisamide.

14. CBD for use according to claim 13, wherein the one or more AED is selected from the group consisting of: sodium valproate; lamotrigine; ethosuximide; clobazam; and clonazepam.

15. CBD for use according to any of the preceding claims, wherein the number of different anti-epileptic drugs that are used in combination with the CBD is reduced.

16. CBD for use according to any of the preceding claims, wherein the dose of anti-epileptic drugs that are used in combination with the CBD is reduced.

17. CBD for use according to any of the preceding claims, wherein the dose of CBD is greater than 5 mg/kg/day.

18. CBD for use according to any of the preceding claims, wherein the epilepsy is childhood epilepsy.

19. A method of treating epilepsy comprising administering cannabidiol (CBD) to a subject, wherein the epilepsy is characterised by absence seizures.

20. A composition for use in the treatment of epilepsy characterised by absence seizures comprising cannabidiol (CBD), a solvent, a co-solvent, a sweetener, and a flavouring.

21. A composition according to claim 20, wherein the solvent is sesame oil.

22. A composition according to claim 20, wherein the co-solvent is ethanol.

23. A composition according to claim 20, wherein the sweetener is sucralose.

24. A composition according to claim 20, wherein the flavouring is strawberry flavour.

25. A composition according to claim 20, wherein the CBD is present at a concentration of between 25/mg/ml and 100 mg/ml.

26. A composition according to any of claims 14 to 19, which comprises cannabidiol (CBD) at a concentration substantially of between 25 to 100 mg/ml, ethanol at a concentration substantially of 79 mg/ml, sucralose at a concentration substantially of 0.5 mg/ml, strawberry flavouring at a concentration substantially of 0.2 mg/ml and sesame q.s. to 1.0ml.

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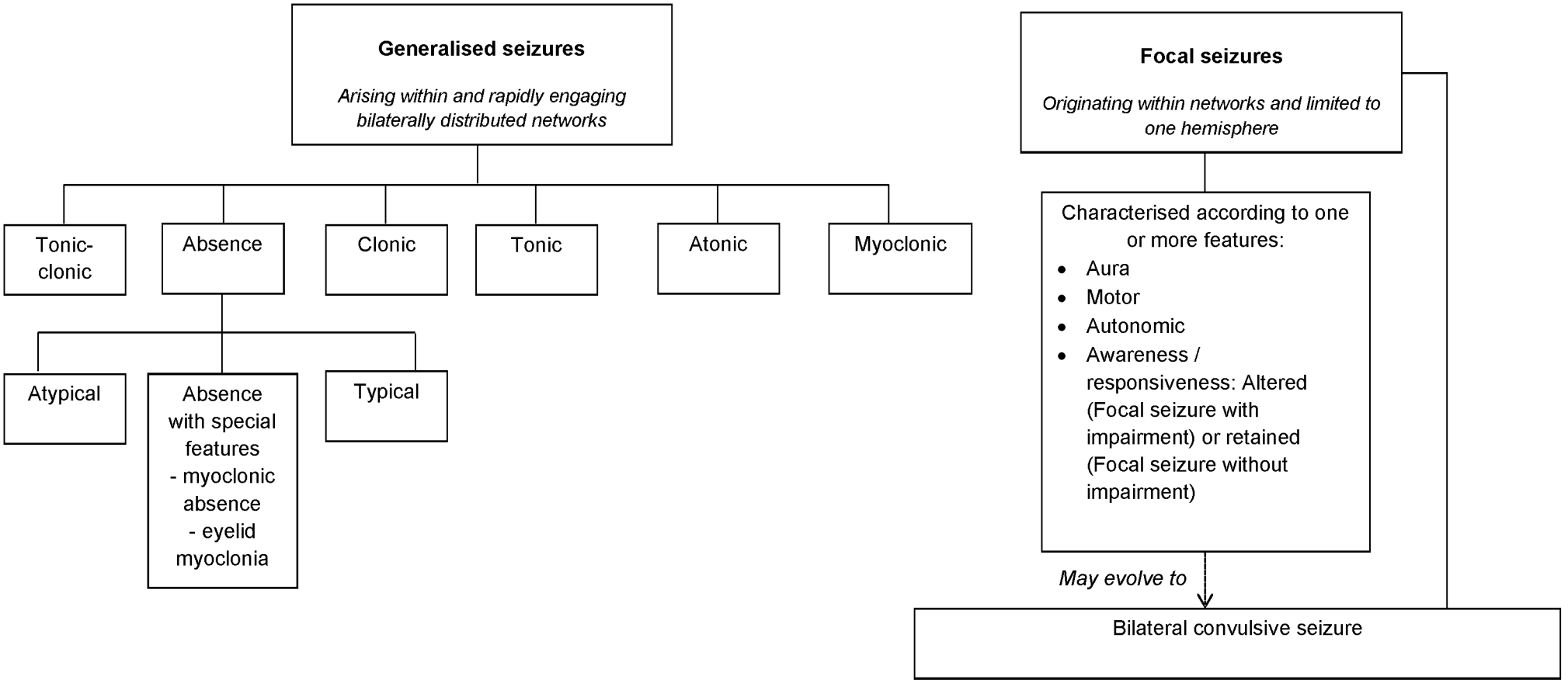
Figure 1. ILAE Proposal for Revised Terminology for Organisation of Seizures and Epilepsies 2010



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/051776

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/05 A61K31/195 A61K31/20 A61K31/27 A61K31/352
A61K31/4015 A61K31/4166 A61K31/423 A61K31/496 A61K31/53
A61K31/551 A61K31/5513 A61K31/5517 A61K31/7048 A61P25/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PORTER BRENDA E ET AL: "Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy", EPILEPSY AND BEHAVIOR, vol. 29, no. 3, 10 May 2013 (2013-05-10), pages 574-577, XP028775189, ISSN: 1525-5050, DOI: 10.1016/J.YEBEH.2013.08.037 the whole document ----- -/--	1-26

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2015	25/08/2015

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	EDWARD MAA ET AL: "The case for medical marijuana in epilepsy", EPILEPSIA, vol. 55, no. 6, 1 June 2014 (2014-06-01), pages 783-786, XP055205357, ISSN: 0013-9580, DOI: 10.1111/epi.12610 the whole document	1-26
Y	WO 2012/093255 A1 (GW PHARMA LTD [GB]; OTSUKA PHARMA CO LTD [JP]; WHALLEY BENJAMIN [GB];) 12 July 2012 (2012-07-12) paragraph [0017]; claims 5,6	1-26
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X,P	CRAIG A. PRESS ET AL: "Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy", EPILEPSY & BEHAVIOR, vol. 45, 1 April 2015 (2015-04-01), pages 49-52, XP055205370, ISSN: 1525-5050, DOI: 10.1016/j.yebeh.2015.02.043 the whole document	1-26

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2015/051776

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