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(71) Applicant(s):
GW Research Limited
Sovereign House, Vision Park Chivers Way, Histon, Cambridge, Cambridgeshire, CB24 9BZ, United Kingdom

(72) Inventor(s):
Daniel Adam Checketts
Kevin James Craig

(74) Agent and/or Address for Service:
HGF Limited
Document Handling - HGF - (Manchester), 1 City Walk, LEEDS, LS11 9DX, United Kingdom

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(54) Title of the Invention: **Use of cannabidiol in the treatment of seizures associated with herpes simplex virus**
Abstract Title: **Use of cannabidiol for the treatment of seizures associated with herpes simplex virus**

(57) The use of cannabidiol (CBD) for the treatment of seizures associated with herpes simplex virus. The types of seizures may include tonic, tonic-clonic, atonic, myoclonic, absence and focal seizures with impairment. The CBD preparation may comprise 95% (w/w) CBD and not more than 0.15% (w/w) tetrahydrocannabinol (THC). Preferably the CBD preparation comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) other cannabinoids, which may comprise THC, cannabidiol-C1 (CBC-C1), cannabidivarin (CBDV), and cannabidiol-C4 (CBD-C4), where the THC may be a mixture of trans-THC and cis-THC. The CBD preparation may be used in combination with one or more concomitant anti-epileptic drugs (AEDs) such as valproic acid, levetiracetam, clobazam, zonisamide, rufinamide, topiramate, lamotrigine, lacosamide, ethosuximide, phenobarbital, oxcarbazepine, N-desmethylclobazam, phenytoin, felbamate, diazepam, and gabapentin. The CBD in the CBD preparation may be synthetic or isolated from cannabis plant material. Preferably the dose of CBD is between 5 mg/kg/day to 50 mg/kg/day.

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USE OF CANNABIDIOL IN THE TREATMENT OF SEIZURES ASSOCIATED WITH HERPES SIMPLEX VIRUS

FIELD OF THE INVENTION

[0001] The present invention relates to the use of cannabidiol (CBD) for the treatment of seizures associated with herpes simplex virus. In a further embodiment the types of seizures include tonic, tonic-clonic, atonic, myoclonic, absence and focal seizures with impairment. Preferably the dose of CBD is between 5 mg/kg/day to 50 mg/kg/day.

[0002] In a further embodiment the CBD used is in the form of a highly purified extract of cannabis such that the CBD is present at greater than 95% of the total extract (w/w) and the cannabinoid tetrahydrocannabinol (THC) has been substantially removed, to a level of not more than 0.15% (w/w).

[0003] Preferably the CBD used is in the form of a botanically derived purified CBD which comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) of other cannabinoids. More preferably the other cannabinoids present are THC at a concentration of less than or equal to 0.1% (w/w); CBD-C1 at a concentration of less than or equal to 0.15% (w/w); CBDV at a concentration of less than or equal to 0.8% (w/w); and CBD-C4 at a concentration of less than or equal to 0.4% (w/w). The botanically derived purified CBD preferably also comprises a mixture of both trans-THC and cis-THC. Alternatively, a synthetically produced CBD is used.

[0004] Where the CBD is given concomitantly with one or more other 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.

BACKGROUND TO THE INVENTION

[0005] 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).

[0006] 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).

[0007] 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.

[0008] 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.

[0009] 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.

[0010] 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.

[0011] Generalized 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.

[0012] 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).

[0013] 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.

[0014] Infection with herpes simplex virus (HSV) can be due to either herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2). The two viruses are members of the human *Herpesviridae* family, a set of viruses that produce viral infections in the majority of humans.

[0015] HSV-1 is mainly transmitted by oral-to-oral contact to cause infection in or around the mouth but can also be transmitted through oral-genital contact to cause infection in or

around the genital area. HSV-2 is almost exclusively transmitted through genital-to-genital contact during sex, causing infection in the genital or anal area.

[0016] Both oral herpes infections and genital herpes infections are mostly asymptomatic or unrecognized but can cause symptoms of painful blisters or ulcers at the site of infection, ranging from mild to severe.

[0017] Treatment for HSV include antiviral medications, such as acyclovir, famciclovir, and valacyclovir. These can help to reduce the severity and frequency of symptoms but cannot cure the infection.

[0018] When HSV enters the brain, a person can develop herpes simplex virus encephalitis (HSE), a type of infectious encephalitis that is rare and often severe. Typically, the virus is initially present in the limbic cortex of the brain and then may spread to the adjacent frontal and temporal lobes of the brain. The destruction of tissue in these areas together with brain swelling from the inflammation causes many of the symptoms.

[0019] The onset of HSE may vary dependent on the patient's immunity but usually develops over a period of days. Typically, it begins with 'flu-like' symptoms followed by neurological deterioration. The most common symptoms include headache; confusion; nausea; fever; seizures; drowsiness. If left untreated, the symptoms become increasingly worse and can ultimately lead to death.

[0020] The prognosis of HSE has become better with more patients living to adulthood, but many may suffer from permanent neurological and psychological deficits, for example amnesia.

[0021] Prompt treatment of individuals with HSE is important as it improves the efficiency of treatment options. Treatment with the antiviral drugs acyclovir and vidarabine have been reported to improve symptoms in individuals with HSE. However, antiviral therapy may not benefit affected individuals in advanced stages of the infection. Seizures associated with HSE may be treated with anticonvulsants.

[0022] Cannabidiol (CBD), a non-psychoactive derivative from the cannabis plant, has demonstrated anti-convulsant properties in several anecdotal reports, pre-clinical and clinical studies both in animal models and humans. Three randomized control trials showed efficacy of the purified pharmaceutical formulation of CBD in patients with Dravet and Lennox-Gastaut syndrome.

[0023] Based on these three trials, a botanically derived purified CBD preparation was approved by FDA in June 2018 for the treatment of seizures associated with Dravet and Lennox-Gastaut syndromes.

[0024] In 2010 a review by NYU Cancer Institute reported on how cannabinoids could be used to fight against infections including herpes simplex virus.[1] However there is no indication of the types of seizures that could be treated and not even whether CBD can be effective in reducing seizures associated with herpes simplex virus.

[0025] A review by Tagne *et al.* in 2020 examined the current state of knowledge on the use of CBD in viral diseases.[2] Again, there is no mention nor any suggestion of the types of seizures that could be treated nor the effectiveness of CBD in reducing seizures associated with herpes simplex virus.

[0026] The applicant has found by way of an open label, expanded-access program that treatment with CBD resulted in a significant reduction in tonic, tonic-clonic, atonic, myoclonic, absence and focal seizures with impairment in patients with herpes simplex virus.

BRIEF SUMMARY OF THE DISCLOSURE

[0027] In accordance with a first aspect of the present invention there is provided a cannabidiol (CBD) preparation for use in the treatment of herpes simplex virus.

[0028] In a further embodiment, the seizures associated with herpes simplex virus are tonic, tonic-clonic, atonic, myoclonic, absence and focal seizures with impairment.

[0029] In a further embodiment, the CBD preparation comprises greater than 95% (w/w) CBD and not more than 0.15% (w/w) tetrahydrocannabinol (THC).

[0030] Preferably the CBD preparation comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) other cannabinoids, wherein the less than or equal to 2% (w/w) other cannabinoids comprise the cannabinoids tetrahydrocannabinol (THC); cannabidiol-C1 (CBD-C1); cannabidivarin (CBDV); and cannabidiol-C4 (CBD-C4), and wherein the THC is present as a mixture of trans-THC and cis-THC.

[0031] Preferably the CBD preparation is used in combination with one or more concomitant anti-epileptic drugs (AED).

[0032] Preferably the one or more AED is selected from the group consisting of: valproic acid, levetiracetam, clobazam, zonisamide, rufinamide, lacosamide, topiramate, lamotrigine, ethosuximide, phenobarbital, oxcarbazepine, N-desmethylclobazam, phenytoin, felbamate, diazepam and gabapentin.

[0033] In one embodiment the CBD is present is isolated from cannabis plant material. Preferably at least a portion of at least one of the cannabinoids present in the CBD preparation is isolated from cannabis plant material.

[0034] In a further embodiment the CBD is present as a synthetic preparation. Preferably at least a portion of at least one of the cannabinoids present in the CBD preparation is prepared synthetically.

[0035] Preferably the dose of CBD is greater than 5 mg/kg/day. More preferably the dose of CBD is 20 mg/kg/day. More preferably the dose of CBD is 25 mg/kg/day. More preferably the dose of CBD is 50 mg/kg/day.

[0036] In accordance with a second aspect of the present invention there is provided a method of treating seizures associated with herpes simplex virus comprising administering a cannabidiol (CBD) preparation to the subject in need thereof.

DEFINITIONS

[0037] Definitions of some of the terms used to describe the invention are detailed below:

[0038] Over 100 different cannabinoids have been identified, see for example, Handbook of Cannabis, Roger Pertwee, Chapter 1, pages 3 to 15. 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).

[0039] "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.

[0040] "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.

[0041] "Synthetic cannabinoids" are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.

[0042] 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.

[0043] "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.

[0044] "Tonic seizures" can be generalised onset, affecting both sides of the brain, or they can be focal onset, starting in just one side of the brain. If a tonic seizure starts in both sides of the brain, all muscles tighten and the subject's body goes stiff. If standing, they may fall to the

floor, their neck may extend, eyes open wide and roll upwards, whilst their arms may raise upwards and legs stretch or contract. If a tonic seizure starts in one side of the brain muscles tighten in just one area of the body. Tonic seizures usually last less than one minute.

[0045] "Tonic-clonic seizures" consist of two phases: the tonic phase and the clonic phase. In the tonic phase the body becomes entire rigid, and in the clonic phase there is uncontrolled jerking. Tonic-clonic seizures may or may not be preceded by an aura, and are often followed by headache, confusion, and sleep. They may last mere seconds or continue for several minutes. These seizures are also known as a grand mal seizure.

[0046] "Atonic seizures" occur when a person suddenly loses muscle tone so their head or body may go limp. They are also known as drop attacks. In some children, only their head drops suddenly. They can begin in one area or side of the brain (focal onset) or both sides of the brain (generalized onset).

[0047] "Myoclonic seizures" are characterised by a 'muscle jerk'. Myoclonic seizures are brief but can happen in clusters (many happening close together in time) and often happen shortly after waking. In myoclonic seizures the person is conscious, but they are classified as generalised seizures.

[0048] "Absence seizures" also may be called "petit mal" seizures. These types of seizure cause a loss of awareness for a short time. They mainly affect children although can happen at any age. During an absence seizure, a person may: stare blankly into space; look like they're "daydreaming"; flutter their eyes; make slight jerking movements of their body or limbs. The seizures usually only last up to 15 seconds and may occur several times a day.

[0049] "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.

[0050] "Focal seizure with impairment" 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.

DETAILED DESCRIPTION

PREPARATION OF HIGHLY PURIFIED CBD EXTRACT

[0051] The following describes the production of the highly-purified (>95% w/w) cannabidiol extract which has a known and constant composition.

[0052] In summary the drug substance used 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. Although the CBD is highly purified because it is produced from a cannabis plant rather than synthetically there is a small number of other cannabinoids which are co-produced and co-extracted with the CBD. Details of these cannabinoids and the quantities in which they are present in the medication are as described in Table A below.

Table A: Composition of highly purified CBD extract

Cannabinoid	Concentration
CBD	> 95% w/w
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

> – greater than

NMT – not more than

PREPARATION OF BOTANICALLY DERIVED PURIFIED CBD

[0053] The following describes the production of the botanically derived purified CBD which comprises greater than or equal to 98% w/w CBD and less than or equal to other cannabinoids was used in the open label, expanded-access program described in Example 1 below.

[0054] 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.

[0055] 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 (botanically derived purified CBD).

[0056] 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.

[0057] All parts of the process are controlled by specifications. The botanical raw material specification is described in Table B and the CBD API is described in Table C.

Table B: CBD botanical raw material specification

Test	Method	Specification
Identification: -A -B -C	 Visual TLC HPLC/UV	 Complies Corresponds to standard (for CBD & CBDA) Positive for CBDA
Assay: CBDA + CBD	In-house (HPLC/UV)	NLT 90% of assayed cannabinoids by peak area
Loss on Drying	Ph.Eur.	NMT 15%
Aflatoxin	UKAS method	NMT 4ppb
Microbial: - TVC - Fungi - E.coli	Ph.Eur.	NMT 10^7cfu/g NMT 10^5cfu/g NMT 10^2cfu/g
Foreign Matter:	Ph.Eur.	NMT 2%
Residual Herbicides and Pesticides	Ph.Eur.	Complies

Table C: Specification of an exemplary botanically derived purified CBD preparation

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 %
CBDA CBDV THC CBD-C4	HPLC-UV	NMT 0.15% w/w NMT 1.0% w/w NMT 0.1% 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

[0058] The purity of the botanically derived purified CBD preparation was greater than or equal to 98%. The botanically derived purified CBD includes THC and other cannabinoids, e.g., CBDA, CBDV, CBD-C1, and CBD-C4.

[0059] Distinct chemotypes of the *Cannabis sativa* L. plant have been produced to maximize the output of the specific chemical constituents, the cannabinoids. Certain chemovars produce predominantly CBD. Only the (-)-trans isomer of CBD is believed to occur naturally. During purification, the stereochemistry of CBD is not affected.

Production of CBD botanical drug substance

[0060] An overview of the steps to produce a botanical extract, the intermediate, are as follows:

a) Growing
b) Direct drying
c) Decarboxylation
d) Extraction - using liquid CO_2
e) Winterization using ethanol
f) Filtration

g) Evaporation

[0061] High CBD chemovars were grown, harvested, dried, baled 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 prior to extraction.

[0062] Decarboxylation of CBDA to CBD was carried out using heat. BRM was decarboxylated at 115ºC for 60 minutes.

[0063] Extraction was performed using liquid CO_2 to produce botanical drug substance (BDS), which was then crystalized to produce the test material. The crude CBD BDS was winterized to refine the extract under standard conditions (2 volumes of ethanol at -20°C for approximately 50 hours). The precipitated waxes were removed by filtration and the solvent was removed to yield the BDS.

Production of botanically derived purified CBD preparation

[0064] The manufacturing steps to produce the botanically derived purified CBD preparation from BDS were as follows:

a) Crystallization using C_5-C_{12} straight chain or branched alkane
b) Filtration
c) Vacuum drying

[0065] The BDS produced using the methodology above was dispersed in C_5-C_{12} straight chain or branched alkane. 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 via vacuum filtration, washed with aliquots of cold C_5-C_{12} straight chain or branched alkane, and dried under a vacuum of <10mb at a temperature of 60°C until dry. The botanically derived purified CBD preparation was stored in a freezer at -20°C in a pharmaceutical grade stainless steel container, with FDA food grade approved silicone seal and clamps.

Physicochemical properties of the botanically derived purified CBD

[0066] The botanically derived purified CBD used in the clinical trial described in the invention comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) of other cannabinoids. The other cannabinoids present are THC at a concentration of less than or equal to 0.1% (w/w); CBD-C1 at a concentration of less than or equal to 0.15% (w/w); CBDV at a concentration of less than or equal to 0.8% (w/w); and CBD-C4 at a concentration of less than or equal to 0.4% (w/w).

[0067] The botanically derived purified CBD used additionally comprises a mixture of both trans-THC and cis-THC. It was found that the ratio of the trans-THC to cis-THC is altered and can be controlled by the processing and purification process, ranging from 3.3:1 (trans-THC:cis-THC) in its unrefined decarboxylated state to 0.8:1 (trans-THC:cis-THC) when highly purified.

[0068] Furthermore, the cis-THC found in botanically derived purified CBD is present as a mixture of both the (+)-cis-THC and the (-)-cis-THC isoforms.

[0069] Clearly a CBD preparation could be produced synthetically by producing a composition with duplicate components.

[0070] Example 1 below describes the use of a botanically derived purified CBD in an open label, expanded-access program to investigate the clinical efficacy and safety of purified pharmaceutical cannabidiol formulation (CBD) in the treatment of herpes simplex virus.

EXAMPLE 1: CLINICAL EFFICACY AND SAFETY OF PURIFIED PHARMACEUTICAL CANNABIDIOL (CBD) IN THE TREATMENT OF PATIENTS DIAGNOSED WITH HERPES SIMPLEX VIRUS

Study design

[0071] Subjects were required to be on one or more AEDs at stable doses for a minimum of two weeks prior to baseline and to have stable vagus nerve stimulation (VNS) settings and ketogenic diet ratios for a minimum of four weeks prior to baseline.

[0072] Patients were administered botanically derived purified CBD in a 100 mg/mL sesame oil-based solution.

[0073] A maximum dose of 50 mg/kg/day could be utilised for patients who were tolerating the medication but had not achieved seizure control; these patients had further weekly titration by 5mg/kg/day.

[0074] There were six patients in this study, and each received CBD for various durations of time. Modifications were made to concomitant AEDs as per clinical indication.

[0075] Seizure frequency, intensity, and duration were recorded by caregivers in a diary during a baseline period of at least 28 days. Changes in seizure frequency relative to baseline were calculated after at least 2 weeks and at defined timepoints of treatment.

Statistical Methods:

[0076] Patients may be defined as responders if they had more than 50% reduction in seizure frequency compared to baseline. The percent change in seizure frequency was calculated as follows:

$$\text{seizure frequency \% change} = \frac{(\text{weekly seizure frequency } \textit{time interval}) - (\text{weekly seizure frequency } \textit{Baseline})}{(\text{weekly seizure frequency } \textit{Baseline})} \times 100$$

[0077] The percent change of seizure frequency may be calculated for any time interval where seizure number has been recorded. For the purpose of this example the percent change of seizure frequency for the end of the treatment period was calculated as follows:

$$\text{seizure frequency \% reduction} = \frac{(\text{weekly seizure frequency } \textit{Baseline}) - (\text{weekly seizure frequency } \textit{End})}{(\text{weekly seizure frequency } \textit{Baseline})} \times 100$$

Results

Patient description

[0078] The six patients enrolled in the open label, expanded-access program were diagnosed with herpes simplex virus. These patients experienced several different seizure types including tonic, tonic-clonic, atonic, myoclonic, absence and focal seizures with impairment and were taking several concomitant AEDs.

[0079] The age of patients ranged from 7-24 years, three were male and three were female as detailed in Table 1 below.

Table 1: Patient demographics, seizure type and concomitant medication

Patient Number	Age (years)	Sex	Seizure types	Concomitant AEDs
1	7.47	M	Tonic-clonic, myoclonic, absence, focal with impairment	CLB, VPA, ETH

2	11.24	F	Tonic, tonic-clonic, atonic, absence, focal without impairment	CLB, LEV, TPM, LCS, PHB
3	17.23	F	Tonic-clonic, myoclonic	LTG, OXC, ZNS
4	24.27	F	Tonic-clonic, atonic, focal with impairment	CLB, N-DMC, LCS, PHT
5	14.07	M	Tonic-clonic, atonic, myoclonic, absence	CLB, RFN, LTG, PHT
6	8.34	M	Tonic	CLB, LEV, TPM, FLB, DZP, GBP

VPA = valproic acid, LEV = levetiracetam, CLB = clobazam, ZNS = zonisamide, RFN = rufinamide, LCS = lacosamide, TPM = topiramate, LTG = lamotrigine, ETH = ethosuximide, PHB = phenobarbital, OXC = oxcarbazepine, N-DMC = N-desmethylclobazam, PHT = phenytoin, FLB = felbamate, DZP = diazepam, GBP = gabapentin

Study medication and concomitant medications

[0080] Patients on the study were titrated up to various doses of CBD.

[0081] The average number of concomitant AEDs at the time of starting CBD was four per patient (range: 3-6, median: 4).

Clinical changes

[0082] Tables 2A-F illustrate the seizure frequency for each patient as well as the dose of CBD given.

Table 2A: Seizure frequency data for Patient 1

Patient 1					
Time	**Seizure Type**				**Dose CBD (mg/kg/day)**
	Tonic-clonic	**Myoclonic**	**Absence**	**Focal with impairment**	
Baseline	0.0	75.0	2500.0	100.0	-
4 weeks	14.0	4.0	800.0	14.0	5.0
8 weeks	20.0	0.0	1390.0	12.0	10.0
16 weeks	20.0	0.0	250.0	7.0	15.0
24 weeks	79.6	0.0	398.0	0.0	20.0
36 weeks	31.3	0.0	466.6	0.0	25.0

48 weeks	16.0	0.0	231.7	0.0	25.0

[0083] Patient 1 was treated for 48 weeks and experienced a 100% reduction in myoclonic seizures, a 90.7% reduction in absence seizures and a 100% reduction in focal seizures with impairment over the treatment period.

Table 2B: Seizure frequency data for Patient 2

Patient 2					
Time	**Seizure Type**				**Dose CBD (mg/kg/day)**
	Tonic	**Tonic-clonic**	**Absence**	**Focal without impairment**	
Baseline	32.0	1.0	8.0	8.0	25.0
4 weeks	44.0	0.0	6.0	8.0	25.0
8 weeks	24.0	0.0	0.0	0.0	25.0
24 weeks	56.0	0.5	12.0	17.0	25.0

[0084] Patient 2 was treated for 24 weeks and experienced a 50% reduction in tonic-clonic seizures over the treatment period.

Table 2C: Seizure frequency data for Patient 3

Patient 3			
Time	**Seizure Type**		**Dose CBD (mg/kg/day)**
	Tonic-clonic	**Myoclonic**	
Baseline	6.0	32.0	-
2 weeks	8.0	6.0	5.0
4 weeks	5.3	9.3	10.0
8 weeks	6.0	16.0	20.0
16 weeks	11.0	4.0	25.0
36 weeks	2.6	9.3	30.0

48 weeks	7.7	18.4	35.0
60 weeks	6.6	19.4	35.0
72 weeks	3.4	9.7	30.0
96 weeks	1.0	13.8	30.0
108 weeks	0.9	13.8	30.0

[0085] Patient 3 was treated for 108 weeks and experienced an 85% reduction in tonic-clonic seizures and a 56.9% reduction in myoclonic seizures over the treatment period.

Table 2D: Seizure frequency data for Patient 4

Patient 4				
Time	**Seizure Type**			**Dose CBD (mg/kg/day)**
	Tonic-clonic	**Atonic**	**Focal with impairment**	
Baseline	10.0	20.0	14.0	-
2 weeks	2.0	0.0	4.0	5.0
4 weeks	2.0	1.0	2.0	10.0
8 weeks	0.0	0.0	0.0	20.0
12 weeks	0.0	5.0	0.0	20.0
16 weeks	0.7	14.0	2.7	15.0
24 weeks	10.0	13.0	3.0	15.0

[0086] Patient 4 was treated for 24 weeks and experienced a 35% reduction in atonic seizures and a 78.6% reduction in focal seizures with impairment over the treatment period.

Table 2E: Seizure frequency data for Patient 5

Patient 5					
Time	**Seizure Type**				**Dose CBD (mg/kg/day)**
	Tonic-clonic	**Atonic**	**Myoclonic**	**Absence**	

Baseline	71.0	748.0	59.0	28.0	5.0
4 weeks	75.0	965.0	75.0	45.0	20.0
8 weeks	7.0	8.0	60.0	0.0	25.0
12 weeks	4.0	25.0	1.0	0.0	25.0
16 weeks	10.0	53.0	0.0	0.0	25.0
24 weeks	40.0	27.2	68.0	0.0	30.0
36 weeks	76.0	44.0	129.0	0.0	40.0
60 weeks	137.0	45.0	184.0	0.0	50.0
72 weeks	130.0	46.3	141.0	3.0	50.0
84 weeks	77.0	39.3	81.0	5.7	30.0
96 weeks	72.0	97.0	41.0	8.0	45.0
108 weeks	53.0	92.0	64.0	11.0	45.0
120 weeks	44.3	72.3	53.0	11.3	45.0
132 weeks	40.4	128.0	66.4	18.8	45.0
144 weeks	18.0	78.4	78.0	49.6	45.0

[0087] Patient 5 was treated for 144 weeks and experienced a 76.4% reduction in tonic-clonic seizures and an 89.5% reduction in atonic seizures over the treatment period.

Table 2F: Seizure frequency data for Patient 6

Patient 6		
Time	**Seizure Type**	**Dose CBD (mg/kg/day)**
	Tonic	
Baseline	24.0	-
2 weeks	40.0	5.0
4 weeks	20.0	10.0
8 weeks	32.0	20.0
12 weeks	12.0	25.0
24 weeks	15.2	25.0
36 weeks	15.2	25.0
48 weeks	18.0	25.0

60 weeks	19.2	25.0

[0088] Patient 6 was treated for 60 weeks and experienced a 20% reduction in tonic seizures over the treatment period.

[0089] Overall, patients reported reductions of 20-100% in seizures over period of treatment with CBD.

[0090] Significantly, patient 1 became completely seizure free in their myoclonic and focal seizures with impairment after 8 and 24 weeks of treatment with CBD respectively.

[0091] CBD was effective in reducing the frequency of the following seizure types: tonic, tonic-clonic, atonic, myoclonic, absence and focal seizures with impairment.

Conclusions

[0092] These data indicate that CBD was able to significantly reduce the number of seizures associated with herpes simplex virus. Clearly the treatment is of significant benefit in this difficult to treat epilepsy syndrome given the high response rate experienced in all patients.

[0093] Of interest is that patients with focal seizures with impairment (patients 1 and 4) obtained significant benefit.

[0094] In conclusion, this study signifies the use of CBD for treatment of seizures associated with herpes simplex virus. Seizure types include tonic, tonic-clonic, atonic, myoclonic, absence and focal seizures with impairment for which seizure frequency rates decreased by significant rates, by 20-100%.

References

1. Reiss. NYU Cancer Institute. (2010) “Cannabinoids and Viral Infections.” Pharmaceuticals (Basel).
2. Tagne *et al*. (2020) “Cannabidiol for Viral Diseases: Hype or Hope?” Cannabis and Cannabinoid Research Vol. 5, No. 2.

CLAIMS

1. A cannabidiol (CBD) preparation for use in the treatment of seizures associated with herpes simplex virus.

2. A CBD preparation for use according to claim 1, wherein the seizures associated with herpes simplex virus are tonic, tonic-clonic, atonic, myoclonic, absence and focal seizures with impairment.

3. A CBD preparation for use according to any of the preceding claims, wherein the CBD preparation comprises greater than 95% (w/w) CBD and not more than 0.15% (w/w) tetrahydrocannabinol (THC).

4. A CBD preparation for use according to any of the preceding claims, wherein the CBD preparation comprises greater than or equal to 98% (w/w) CBD and less than or equal to 2% (w/w) other cannabinoids, wherein the less than or equal to 2% (w/w) other cannabinoids comprise the cannabinoids tetrahydrocannabinol (THC); cannabidiol-C1 (CBD-C1); cannabidivarin (CBDV); and cannabidiol-C4 (CBD-C4), and wherein the THC is present as a mixture of trans-THC and cis-THC.

5. A CBD preparation to any of the preceding claims, wherein the CBD preparation is used in combination with one or more concomitant anti-epileptic drugs (AED).

6. A CBD preparation for use according to claim 5, wherein the one or more AED is selected from the group consisting of: valproic acid, levetiracetam, clobazam, zonisamide, rufinamide, lacosamide, topiramate, lamotrigine, ethosuximide, phenobarbital, oxcarbazepine, N-desmethylclobazam, phenytoin, felbamate, diazepam and gabapentin.

7. A CBD preparation for use according to any of the preceding claims, wherein the CBD is present is isolated from cannabis plant material.

8. A CBD preparation for use according to any of the preceding claims, wherein at least a portion of at least one of the cannabinoids present in the CBD preparation is isolated from cannabis plant material.

9. A CBD preparation for use according to claims 1 to 6, wherein the CBD is present as a synthetic preparation.

10. A CBD preparation for use according to claim 9, wherein at least a portion of at least one of the cannabinoids present in the CBD preparation is prepared synthetically.

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

12. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is 20 mg/kg/day.

13. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is 25 mg/kg/day.

14. A CBD preparation for use according to any of the preceding claims, wherein the dose of CBD is 50 mg/kg/day.

15. A method of treating seizures associated with herpes simplex virus comprising administering a cannabidiol (CBD) preparation to the subject in need thereof.

Intellectual Property Office

Application No:	GB2011148.0	**Examiner:**	Dr Richard Wood
Claims searched:	1-15	**Date of search:**	20 January 2021

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1-15	GB 2539472 A (GW RESEARCH) - see especially Example 2.
X	1-15	GB 2531093 A (GW PHARMA) - see especially Examples 1, 3.
X	1-15	GB 2531278 A (GW PHARMA) - see especially Example 1.
X	1-15	GB 2531282 A (GW PHARMA) - see especially Example 1.
X	1-15	GB 2531280 A (GW PHARMA) - see especially Example 1.

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
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&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

A61K

The following online and other databases have been used in the preparation of this search report

WPI, EPODOC, CAS ONLINE

International Classification:

Subclass	Subgroup	Valid From
A61K	0031/05	01/01/2006
A61K	0036/185	01/01/2006