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(54) Title: USE OF CANNABIDIOL IN THE TREATMENT OF ANGELMAN SYNDROME

(57) Abstract: The present invention relates to the use of cannabidiol (CBD) in the treatment of Angelman syndrome (AS). CBD has been shown to be particularly effective in improving anxiety in rodent models of AS. The CBD is preferably substantially pure. It may take 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. Alternatively, the CBD is synthetically produced. Alternatively, the CBD may be used as a botanical drug substance (BDS) from a cannabis plant in which CBD is the predominant cannabinoid. The CBD may also be present in combination with other cannabinoids and non-cannabinoid components such as terpenes. In use the CBD may be used concomitantly with one or more other medicaments. Alternatively, the CBD may be formulated for administration separately, sequentially or simultaneously with one or more medicaments 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.

USE OF CANNABIDIOL IN THE TREATMENT OF ANGELMAN SYNDROME

FIELD OF THE INVENTION

[0001] The present invention relates to the use of cannabidiol (CBD) in the treatment of Angelman syndrome (AS).

[0002] The CBD is preferably substantially pure. It may take 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. Alternatively, the CBD is synthetically produced.

[0003] In a further alternative the CBD may be used as a botanical drug substance (BDS) from a cannabis plant in which CBD is the predominant cannabinoid. In such an embodiment the CBD may be present in combination with other cannabinoids and non-cannabinoid components such as terpenes.

[0004] In use the CBD may be used concomitantly with one or more other medicaments. Alternatively the CBD may be formulated for administration separately, sequentially or simultaneously with one or more medicaments 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

[0005] Angelman syndrome (AS) occurs in approximately 1 in 12,000 to 15,000 individuals and is caused by abnormalities on chromosome 15. Individuals with AS typically show severe to profound learning disability, significant difficulties with mobility and communication in addition to seizures.

[0006] It has been suggested that between 50% and 80% of individuals with AS meet the criteria for autism spectrum disorder.

[0007] Typical characteristics of Angelman syndrome include: delayed development which is usually noticeable from 6-12 months of age; severe language impairment with little or no speech; movement and balance problems (ataxia); frequent seizures (epilepsy) in around 85% of cases; a small head size (microcephaly); sociable behaviour with frequent smiling.

[0008] A genetic anomaly responsible for AS occurs by chance around the time of conception. The UBE3A gene is either absent or malfunctions. A child usually inherits one copy of the UBE3A gene from each parent. Both copies are switched on (active) in most of the

body's tissues. However, in certain areas of the brain, only the gene inherited from the mother is active. In most cases of AS (about 70%), the child's maternal copy of the UBE3A gene is missing, which means there's no active copy of the UBE3A gene in the child's brain.

[0009] Testing compounds for their effectiveness on signs and symptoms of Angelman syndrome is challenging given that this disorder has so many different affected symptom domains.

[0010] The UBE3A mouse model is used to evaluate a compounds effectiveness in the treatment of AS. This model has been shown to recapitulate many of the phenotypic features of AS, including motor dysfunction, increased seizure susceptibility, and hippocampal-dependent learning and memory deficits in mice with the knockout gene.

[0011] The NOR test is used to evaluate cognition, particularly recognition memory, in rodent models of CNS disorders, such as Angelman syndrome. The test is based on the tendency of rodents to spend more time exploring a novel object than a familiar one. The choice to explore the novel object reflects the use of learning and recognition memory.

[0012] The NOR test is conducted in an open field arena with two different kinds of objects. Both objects are generally consistent in height and volume, but are different in shape and appearance. During habituation, the animals are allowed to explore an empty arena. Twenty-four hours after habituation, the animals are exposed to the familiar arena with two identical objects placed at an equal distance. The next day, the mice are allowed to explore the open field in the presence of the familiar object and a novel object to test short-term and long-term recognition memory. The time spent exploring each object and the discrimination index percentage is recorded. This test is useful for assessing cognitive dysfunction in rodent models of AS.

[0013] There is no specific therapy for Angelman syndrome. Medication is usually required to control seizures. Physical and occupational therapies, communication therapy, and behavioral therapies are also important.

[0014] The endocannabinoid system has been linked to physiological progression of autism spectrum disorders, possibly implicating CB1 and CB2 receptors.

[0015] The phytocannabinoids are known to interact with the endocannabinoid system.

[0016] The phytocannabinoid tetrahydrocannabinol (THC) in the form of dronabinol, CB1 agonist, has been used to treat an autistic child (Kurz and Blass, 2010). Problems associated with the use of CB1 agonists are psychoactivity, anxiety and hallucinations.

[0017] Patent application WO 2014/146699 describes the use of CB1 receptor antagonists in the treatment of diseases associated with dendritic abnormalities. Such diseases include AS and RS. The application is exemplified by the use of rimonabant in the FMR1 knockout mouse model which is a model of FXS.

[0018] The CB1 antagonist, rimonabant, has been shown to have serious side effects which limit its use, such as suicide ideation.

[0019] The present application relates to the use of a phytocannabinoid which is neither a CB1 agonist nor antagonist. CBD is known to have a low affinity for the CB1 receptor (Mechoulam *et al*. 2007).

[0020] To date there are no studies of the use of CBD in the treatment of AS. Such symptoms as described above are difficult to treat, therefore many patients with AS have unmet needs with respect to the treatment of their disease.

BRIEF SUMMARY OF THE DISCLOSURE

[0021] In accordance with a first aspect of the present invention there is provided Cannabidiol (CBD) for use in the treatment of Angelman syndrome.

[0022] In this aspect, treatment of Angelman syndrome encompasses the treatment of the condition as a whole, as opposed to the individual symptoms.

[0023] In accordance with a second aspect of the present invention there is provided Cannabidiol (CBD) for use in the treatment of one or more symptoms or characteristics associated with of Angelman syndrome.

[0024] Preferably the symptoms or characteristics associated with Angelman syndrome are one or more of: movement disorders; anxiety and / or cognitive dysfunction.

[0025] In accordance with a third aspect of the present invention there is provided Cannabidiol (CBD) for use in the treatment of movement disorders associated with Angelman syndrome.

[0026] In accordance with a forth aspect of the present invention there is provided Cannabidiol (CBD) for use in the treatment of anxiety associated with Angelman syndrome.

[0027] In accordance with a fifth aspect of the present invention there is provided Cannabidiol (CBD) for use in the treatment of cognitive dysfunction associated with Angelman syndrome.

[0028] In a further embodiment the CBD is for use in combination with one or more concomitant medicaments which may be taken by the patient to treat the condition and / or one or more symptoms associated therewith. Such as, for example, melatonin for sleeping problems, SSRI for depression, anticonvulsants for epilepsy, methylphenidate for ADHD or antipsychotics for aggression or self-harming behaviour. Preferably the one or more concomitant medicaments is an anti-epileptic drug (AED).

[0029] In a preferred embodiment the CBD is substantially pure. The CBD may be 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.

[0030] In an alternative embodiment the CBD is present as a synthetic compound.

[0031] In yet a further embodiment the CBD may be used as a botanical drug substance, as an extract from a cannabis plant in which CBD is the predominant cannabinoid. The CBD may also be present in combination with other cannabinoids and non-cannabinoid components such as terpenes.

[0032] Determining an effective dose in humans will depend on, for example the mode of delivery (e.g. i.v. or oral), the formulation and the bioavailability of the CBD when delivered and might range between 0.1 and 100 mg/kg/day. Furthermore the fact that cannabinoids often show bell-shaped dose response curves makes determining a dose of CBD more difficult.

[0033] Preferably the dose of CBD is greater than 0.1 mg/kg/day. Thus, for a 15 kg patient a dose of greater than 1.5mg of CBD per day would be provided. Doses greater than 1mg/kg/day such as greater than 5/mg/kg/day, greater than 10 mg/kg/day, greater than 15mg/kg/day and greater than 20 mg/kg/day are also envisaged to be effective.

[0034] Preferably the CBD is provided over an extended period; more preferably this period is at least seven days.

[0035] In a further embodiment the CBD may be used as a dietary supplement or food additive in order to improve symptoms in Angelman syndrome.

[0036] In accordance with a sixth aspect of the present invention there is provided a method of treating Angelman syndrome, comprising administering an effective amount of cannabidiol (CBD) to the subject in need thereof.

[0037] Preferably the subject is a human.

[0038] Preferably the symptoms or characteristics associated with Angelman syndrome are one or more of: movement disorders; anxiety and / or cognitive dysfunction.

[0039] In accordance with a seventh aspect of the present invention there is provided a method of treating a movement disorder in an Angelman syndrome subject comprising administering an effective amount of cannabidiol (CBD) to the subject in need thereof.

[0040] Preferably the subject is a human.

[0041] In accordance with a eighth aspect of the present invention there is provided a method of treating anxiety in an Angelman syndrome subject comprising administering an effective amount of cannabidiol (CBD) to the subject in need thereof.

[0042] Preferably the subject is a human.

[0043] In accordance with a ninth aspect of the present invention there is provided a method of treating a cognitive disfunction in an Angelman syndrome subject comprising administering an effective amount of cannabidiol (CBD) to the subject in need thereof.

[0044] Preferably the subject is a human.

[0045] The human equivalent dose (HED) can be estimated using the following formula:

$$\text{HED} = \text{Animal dose (mg/kg)} \textit{ multiplied by } \frac{\text{Animal } K_m}{\text{Human } K_m}$$

The K_m for a mouse is 3, for a rat the K_m is 6 and the K_m for a human is 37.

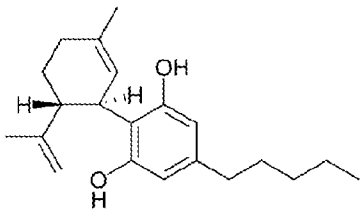
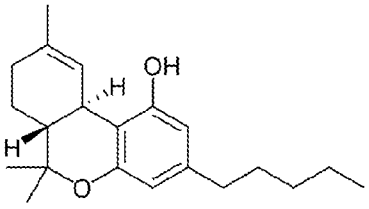
[0046] Furthermore when animal data is obtained using an intraperitoneal form of dosing, but the drug is to be administered using a different delivery method, then the HED calculated may need to be adjusted to take account of the different mode of delivery. In the case of an oral dose the HED may need to be increased in order to obtain an equivalent oral dose, depending on the formulation used, mode of delivery and bioavailability of the active. This is something a skilled pharmacologist will recognise.

DEFINITIONS

[0047] Definitions of some of the terms used to describe the invention are detailed below:

[0048] The cannabinoids described in the present application are listed below along with their standard abbreviations.

Table 1. Cannabinoids and their abbreviations

CBD	Cannabidiol	
THC	Tetrahydrocannabinol	

[0049] 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).

[0050] "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.

[0051] "Substantially pure CBD" is defined as CBD that is greater than 98% (w/w) pure. More preferably greater than 98.5% (w/w) through 99% (w/w) to 99.5% (w/w) and greater.

[0052] "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.

[0053] "Botanical drug substance" or "(BDS)" is defined in the Guidance for Industry Botanical Drug Products Draft Guidance, August 2000, US Department of Health and Human Services, Food and Drug Administration Centre for Drug Evaluation and Research as: "A drug derived from one or more plants, algae, or microscopic fungi. It is prepared from botanical raw materials by one or more of the following processes: pulverisation, decoction, expression, aqueous extraction, ethanolic extraction or other similar processes." A botanical drug substance does not include a highly purified or chemically modified substance derived from natural sources. Thus, in the case of cannabis, BDS derived from cannabis plants do not include highly purified Pharmacopoeial grade cannabinoids. In a BDS comprising cannabinoids the cannabinoid will be present in an amount of less than 95% (w/w).

[0054] "Synthetic cannabinoids" are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.

[0055] 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.

[0056] "Cognitive dysfunction" is defined as the loss of intellectual functions such as thinking, remembering, and reasoning with sufficient severity to interfere with daily functioning. Patients with cognitive dysfunction have trouble with verbal recall, basic arithmetic, and concentration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which

[0058] Figure 1 shows the effect of CBD on clasping duration in a mouse model of Angelman syndrome;

[0059] Figure 2 shows the effect of CBD in the rotarod test in a mouse model of Angelman syndrome;

[0060] Figure 3 shows the effect of CBD in the novel object recognition test in a mouse model of Angelman syndrome; and

[0061] Figure 4 shows the effect of CBD in the tail suspension test in a mouse model of Angelman syndrome.

[0062] Data are expressed as mean ± S.E.M. *p<0.05,***p<0.001 vs WT-vehicle; °°p<0.01,°°°p<0.001 vs KO-vehicle. Two-way ANOVA followed by Bonferroni post hoc test.

DETAILED DESCRIPTION

EXAMPLE 1: USE OF CANNABIDIOL (CBD) IN A MOUSE MODEL OF ANGELMAN SYNDROME

[0063] The effect of CBD was tested in the neurological, behavioural and motor disorders in a transgenic mouse model of Angelman Syndrome.

Materials and Methods

Animals

[0064] Heterozygous mice with maternal deficiency of Ube3A (Ube3am- / p +) and wild type (Ube3am+/p+) were purchased from The Jackson Laboratory (Jackson code: B6.129S7-Ube3a tm1Alb /J) and maintained in a C57BL/6 background.

[0065] Animals were housed under controlled illumination (12:12-hour light/dark cycle; light on 6 hours) and environmental conditions (room temperature: 20°C-22°C, humidity: 55%-60%) with food and tap water were available ad libitum.

Drugs and treatment

[0066] Drugs were dissolved in 1:1:18 ethanol:cremophor:0.9% saline, for intraperitoneal (i.p.) administration. Drug treatment was performed daily for 35 days. CBD was administered at 20 mg/kg.

Behavioural tests

[0067] **Rotarod:** The rotarod test assesses balance and motor coordination of mice. Mice have been measured for the time (in seconds) of equilibrium before falling on a rotary cylinder by a magnet that, activated from the fall of the mouse on the plate, allows to record the time of permanence on the cylinder. After a period of adaptation of 30 s, the spin speed gradually increased from 3 to 30 rpm for a maximum time of 5 min. The animals were analysed by 2 separate tests at 1-h interval in the same day.

[0068] **Clasping:** The clasping test assesses ataxia in mice. Mice were suspended by the base of the tail and their behaviours were recorded for 30 seconds. The time for which the mice clasped their hind limbs was recorded. The time was then scored as follows: 4, 15-30 s, 3, 10-15 s, 2, 5-10 s, 1, 0-5 s and 0,0 s

[0069] **Tail suspension:** The tail suspension test assesses depressive-like behaviour in mice. Mice were individually suspended by the tail on a horizontal bar (50 cm from floor) using adhesive tape placed approximately 4 cm from the tip of the tail. The duration of immobility was recorded in seconds over a period of 6 minutes by a time recorder. Immobility time was defined as the absence of escape-oriented behaviour.

[0070] **Novel Object Recognition**: The novel object recognition assesses recognition memory in mice. The experiment started with the habituation period, during which mice were allowed to freely explore for 1 hour the apparatus which consists of a rectangular open box (40 × 30 × 30 cm width × length × height) made of grey polyvinyl chloride (PVC) illuminated by a dim light. The day after each mouse was allowed to explore two identical objects positioned in the back left and right corners for 5 min (acquisition). A video camera recorded the time spent on exploration of each object. In the test trial, which was carried out for 2 hrs after the acquisition, one of the two objects was replaced with a new different object. The time spent exploring the object was the time that the mouse spent with its nose directed and within 1 cm from the object. The behaviour of mice was analyzed by an observer blind to the treatment. Data are expressed as percentage of recognition index (RI %), which was calculated as the percentage of the time spent exploring the novel object / time spent exploring the novel object + time spent exploring the familiar object x 100.

[0071] Statistical Analysis: Behavioural data are represented as means ± SEM and statistical analysis of these data was performed by two way analysis of variance (ANOVA) for repeated measured followed by the Student Newman--Keuls for multiple comparisons to determine statistical significance between different treated groups of mouse. $p < 0.05$ was considered statistically significant.

Results

[0072] Figure 1 shows that AS mice treated with vehicle showed significantly longer clasping duration at 10 weeks of age compared to WT mice treated with vehicle. In AS mice chronic treatment (30 days) with CBD significantly reduced clasping duration at 10 weeks of age compared to AS mice treated with vehicle.

[0073] Figure 2 demonstrates that AS mice treated with vehicle showed a significant motor impairment at 10 weeks of compared to WT mice treated with vehicle. In AS mice, chronic treatment (30 days) with CBD significantly reduced latency to fall compared to AS mice treated with vehicle.

[0074] Mice were assessed at the age of 7-8 weeks in the novel object recognition test. AS mice treated with vehicle showed a significant decrease in the discrimination index compared with WT mice that received the same treatment. Figure 3 shows that AS mice treated with CBD slightly increased the discrimination index compared to AS mice treated with vehicle.

[0075] Figure 4 shows that in the tail suspension test the time of immobility were significantly higher in AS mice that received vehicle compared to WT mice that received the same treatment. In AS mice treatment with CBD significantly reduced the duration of immobility time compared to AS mice treated with vehicle.

Conclusion

[0076] These data demonstrate that the treatment of 20 mg/kg CBD to mice which were deficient in the Ube3A gene and subsequently suffered symptoms to individuals with AS, were able to reverse these symptoms. In particular CBD was able to statistically significantly improve movement and balance problems (ataxia) and anxiety. As such CBD is considered to be a viable treatment option for AS.

[0077] As is shown in Example 1 above, the use of CBD in a model of Angelman syndrome is able to produce statistically significant reversal of the symptoms associated with this disorder.

[0078] In particular CBD has been shown to produce positive results in the Tail Suspension test in this model and as such demonstrates unequivocally that this phytocannabinoid could reverse anxiety in this disorder.

[0079] In addition, other tests in this model provide support that CBD could be used to treat additional symptoms associated with this disorder as it was able to reduce ataxia and balance and motor coordination symptoms in a model of Angelman syndrome. As such CBD provides a real treatment option to individuals suffering from AS.

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CLAIMS

1. Cannabidiol (CBD) for use in the treatment of Angelman syndrome.

2. Cannabidiol (CBD) for use in the treatment of one or more symptoms or characteristics associated with Angelman syndrome.

3. CBD for use according to claim 2, wherein the symptoms or characteristics associated with Angelman syndrome is a movement disorder.

4. CBD for use according to claim 2, wherein the symptoms or characteristics associated with Angelman syndrome is anxiety.

5. CBD for use according to claim 2, wherein the symptoms or characteristics associated with Angelman syndrome is cognitive dysfunction.

6. Cannabidiol (CBD) for use in the treatment of movement disorder associated with Angelman syndrome.

7. Cannabidiol (CBD) for use in the treatment of anxiety associated with Angelman syndrome.

8. Cannabidiol (CBD) for use in the treatment of cognitive dysfunction associated with Angelman syndrome.

9. CBD for use according to any of the preceding claims, wherein the CBD is for use in combination with one or more concomitant medications.

10. CBD for use according to claim 9, wherein the one or more concomitant medications is an anti-epileptic drug (AED).

11. CBD for use according to any of the preceding claims, wherein the CBD is substantially pure.

12. CBD for use according to claim 11, wherein the CBD is present as a highly purified extract of cannabis which comprises at least 98% (w/w) CBD.

13. CBD for use according to claim 12, wherein the extract comprises less than 0.15% THC.

14. CBD for use according to any of claims 1- 10, where in the CBD is present as a synthetic compound.

15. CBD for use according to any of the preceding claims, wherein the dose of CBD is greater than 0.1 mg/kg/day.

16. A method of treating Angelman syndrome in a subject comprising administering an effective amount of cannabidiol (CBD) to the subject in need thereof.

17. A method as claimed in claim 16 for use in the treatment of one or more symptoms or characteristics associated with Angelman syndrome.

18. A method as claimed in claim 17 wherein the symptoms or characteristics associated with Angelman syndrome is a movement disorder.

19. A method as claimed in claim 17 wherein the symptoms or characteristics associated with Angelman syndrome is anxiety.

20. A method as claimed in claim 17 wherein the symptoms or characteristics associated with Angelman syndrome is a cognitive dysfunction.

21. A method of treating a movement disorder in an Angelman syndrome subject comprising administering an effective amount of cannabidiol (CBD) to the subject in need thereof.

22. A method of treating anxiety in an Angelman syndrome subject comprising administering an effective amount of cannabidiol (CBD) to the subject in need thereof.

23. A method of treating a cognitive disfunction in an Angelman syndrome subject comprising administering an effective amount of cannabidiol (CBD) to the subject in need thereof.

Figure 1: Effect of CBD on clasping duration in a mouse model of Angelman syndrome

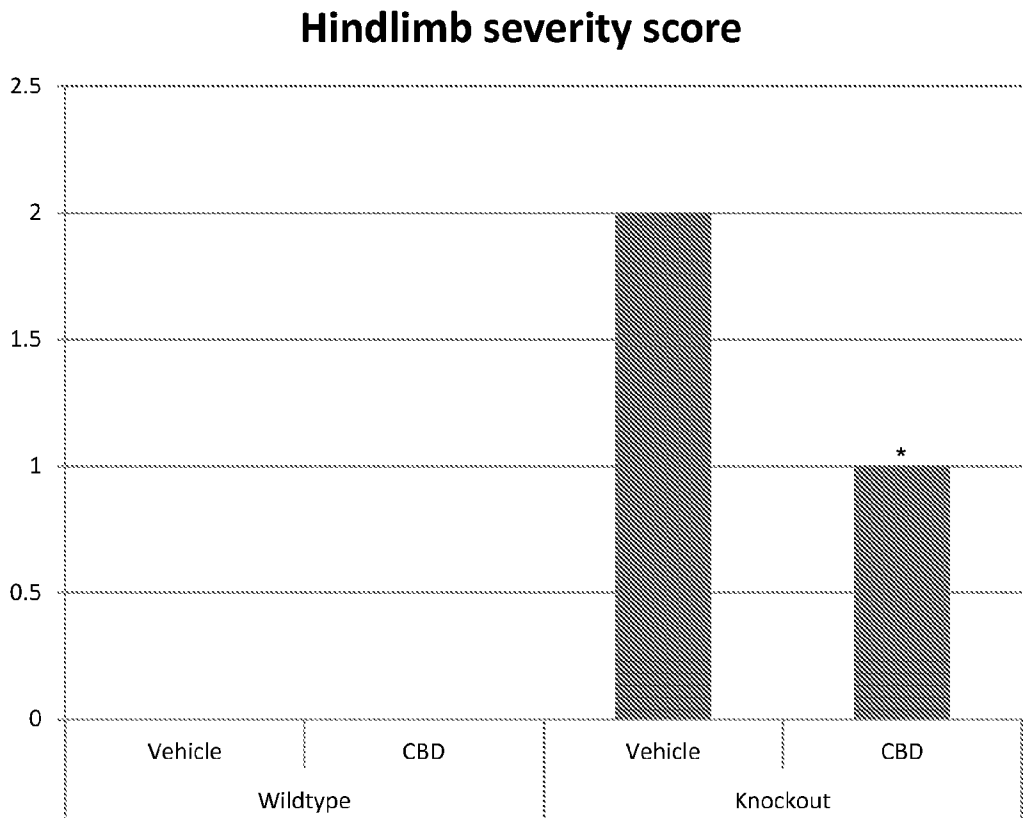


Figure 2: Effect of CBD in the rotarod test in a mouse model of Angelman syndrome

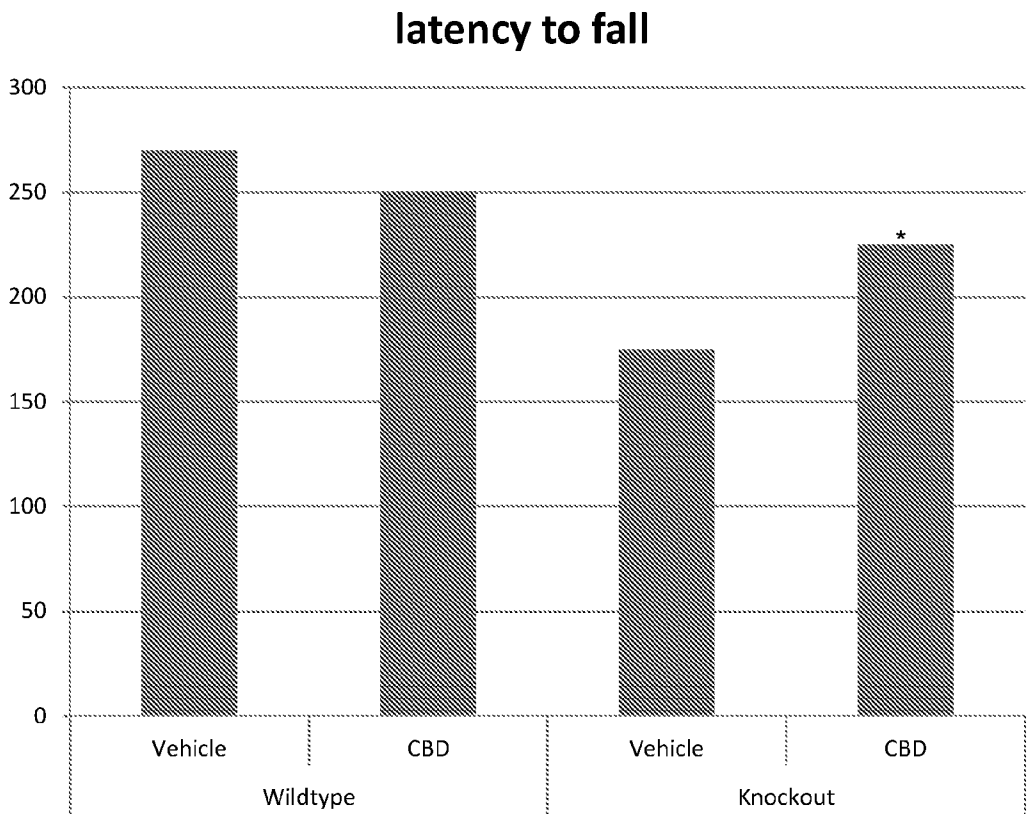


Figure 3: Effect of CBD in the novel object recognition test in a mouse model of Angelman syndrome

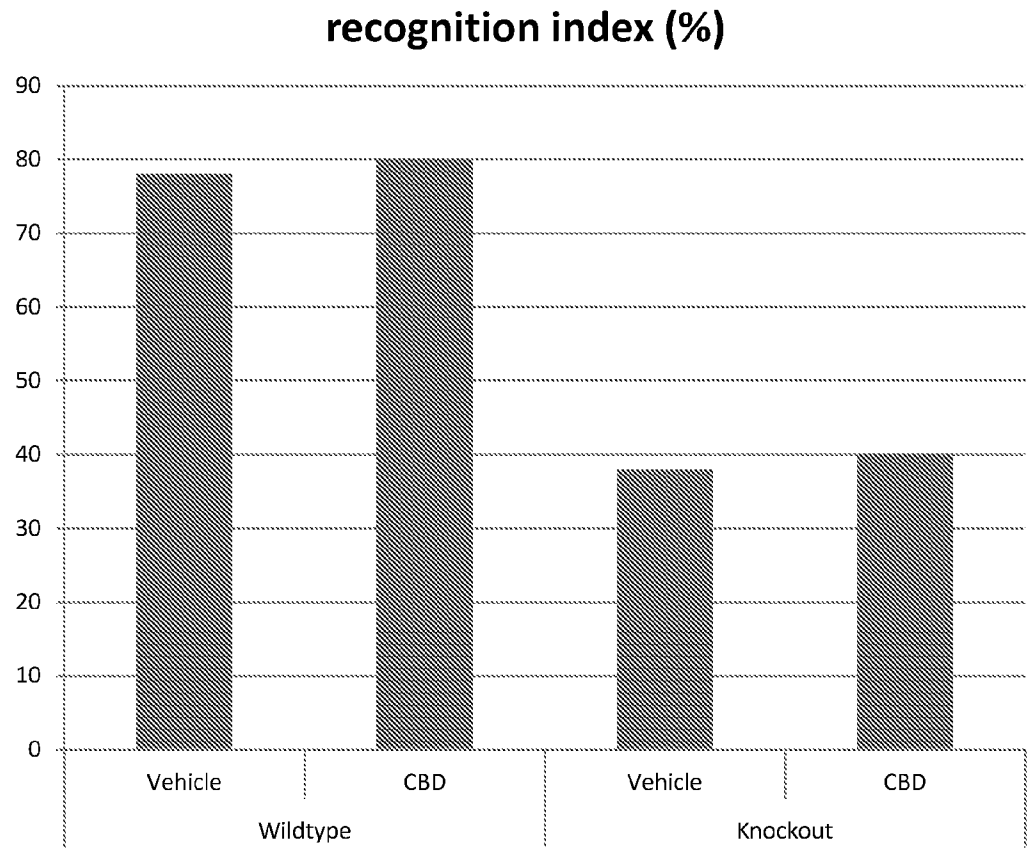
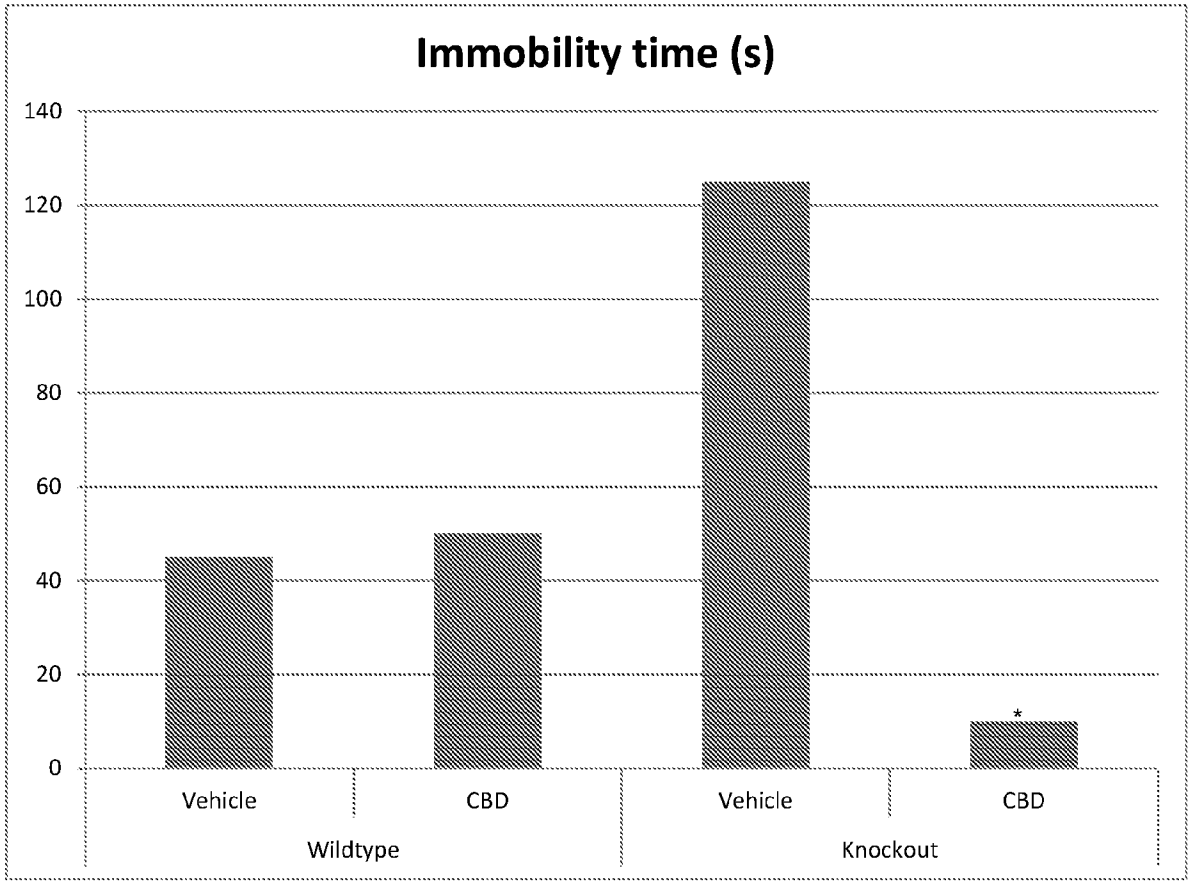


Figure 4: Effect of CBD in the tail suspension test in a mouse model of Angelman syndrome



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/053735

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/352 A61K45/06 A61K36/185 A61P25/00
ADD.

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 A61P

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Grotenhermen: "Epilepsiebehandlung des Angelman-Syndroms mit CBD (Cannabidiol)", , 21 January 2015 (2015-01-21), XP055456120, Retrieved from the Internet: URL:http://s8a85e4d6fcfb04b6.jimcontent.com/download/version/1472724876/module/9873059694/name/Epilepsiebehandlung%20durch%20CBD.pdf [retrieved on 2018-03-02] the whole document	1-23
X	GB 2 531 282 A (GW PHARMA LTD [GB]) 20 April 2016 (2016-04-20) claims 2, 5-6, 8-10, 11	9,10,12, 13,15

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

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 2018	14/03/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ansaldo, M

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/053735

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	GB 2 438 682 A (GW PHARMA LTD [GB]) 5 December 2007 (2007-12-05) claims 1-3, 10,16	2,5,8, 17,20,23
X	US 2016/256411 A1 (AUNG-DIN RONALD [US]) 8 September 2016 (2016-09-08) claims 15-16, 18, 27; table 7	1-8, 17-23

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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