PSILOCYBIN OR PSILOCIN IN COMBINATION WITH CANNABINOID

The present invention relates to the use of one or more cannabinoids in combination with psilocybin and/or psilocin for use in the prevention or treatment of psychological or brain disorders. Preferably the one or more cannabinoids are taken from the group cannabidiol (CBD); cannabidiolic acid (CBD-A); tetrahydrocannabinolic acid (THC-A); tetrahydrocannabivar (THCV); tetrahydrocannabidiol (THC); cannabichromene (CBC); cannabichromenic acid (CBC-A); cannabigerol (CBG) and cannabigerolic acid (CBOA).
PSILOCYBIN OR PSILOCIN IN COMBINATION WITH CANNABINOID

Technical field
The present disclosure provides for psilocybin and/or psilocin in combination with at least one cannabinoid for use in the prevention or treatment of psychological and brain disorders, wherein the at least one cannabinoid is administered separately, sequentially or simultaneously to the psilocybin and/or psilocin.

Background
Depression is a state of low mood and aversion to activity or apathy that can affect a person’s thoughts, behaviour, feelings and sense of well-being.

People with a depressed mood can feel sad, anxious, empty, hopeless, helpless, worthless, guilty, irritable, angry, ashamed or restless. They may lose interest in activities that were once pleasurable, experience loss of appetite or overeating, have problems concentrating, remembering details or making decisions, experience relationship difficulties and may contemplate, attempt or commit suicide. Insomnia, excessive sleeping, fatigue, aches, pains, digestive problems or reduced energy may also be present.

Depressed mood is a feature of some psychiatric syndromes such as major depressive disorder, but it may also be a normal reaction, as long as it does not persist long term, to life events such as bereavement, a symptom of some bodily ailments or a side effect of some drugs and medical treatments. A DSM diagnosis distinguishes an episode (or 'state') of depression from the habitual (or 'trait') depressive symptoms someone can experience as part of their personality.

A number of psychiatric syndromes feature depressed mood as a main symptom. The mood disorders are a group of disorders considered to be primary disturbances of mood. These include major depressive disorder (MDD; commonly called major depression or clinical depression) where a person has at least two weeks of depressed mood or a loss of interest or pleasure in nearly all activities; and dysthymia, a state of chronic depressed mood, the symptoms of which do not meet the severity of a major depressive episode. Another mood disorder, bipolar disorder, features one or more episodes of abnormally elevated mood, cognition and energy levels, but may also involve one or more episodes of depression.
When the course of depressive episodes follows a seasonal pattern, the disorder (major depressive disorder, bipolar disorder, etc.) may be described as a seasonal affective disorder. Outside the mood disorders: borderline personality disorder often features an extremely intense depressive mood; adjustment disorder with depressed mood is a mood disturbance appearing as a psychological response to an identifiable event or stressor, in which the resulting emotional or behavioral symptoms are significant but do not meet the criteria for a major depressive episode; and posttraumatic stress disorder, an anxiety disorder that sometimes follows trauma, is commonly accompanied by depressed mood. Depression is sometimes associated with substance use disorder. Both legal and illegal drugs can cause substance use disorder.

Questionnaires and checklists such as the Beck Depression Inventory or the Children's Depression Inventory can be used by a mental health provider to help detect, and assess the severity of depression. Semi-structured interviews such as the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) and the Structured Clinical Interview for DSM-IV (SCID) are used for diagnostic confirmation of depression.

Schizophrenia is a mental disorder characterized by abnormal social behavior and failure to understand what is real. Common symptoms include false beliefs, unclear or confused thinking, hearing voices that others do not, reduced social engagement and emotional expression, and a lack of motivation. People with schizophrenia often have additional mental health problems such as anxiety disorders, major depressive illness, or substance use disorders. Symptoms typically come on gradually, begin in young adulthood, and last a long time.

Schizophrenia is diagnosed based on criteria in either the American Psychiatric Association's fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5), or the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD-10). These criteria use the self-reported experiences of the person and reported abnormalities in behavior, followed by a clinical assessment by a mental health professional. Symptoms associated with schizophrenia occur along a continuum in the population and must reach a certain severity before a diagnosis is made.

Schizophreniform disorder (acute schizophrenic episode) is characterized by the presence of some of the symptoms of schizophrenia including: delusions, hallucinations, disorganised speech, disorganised or catatonic behaviour, and negative symptoms. The disorder -
including its prodromal, active, and residual phases - lasts longer than 1 month but less than 6 months. Schizoaffective disorder symptoms can vary greatly from patient to patient. Many patients suffer with problems with mood, daily function or intrusive thoughts. Other symptoms can include elevated, inflated or depressed mood; irritability and poor temper control; changes in appetite, energy and sleep; hallucinations (particularly auditory hallucinations); delusions of reference; paranoia; deteriorating concern with hygiene and disorganised or illogical speech.

Schizoaffective disorder features cycles of severe symptoms followed by improvement.

Bipolar I disorder (mania, manic disorder, manicdepressive psychosis) is characterised by mood swings that range from low (feelings of intense depression and despair) to high (feelings of elation, referred to as "mania") and can be mixed, for example a depressed mood may be combined with restlessness and overactivity. Often both depressive and manic episodes are experienced.

Bipolar II disorder is characterised by hypomanic episodes as well as at least one major depressive episode. Hypomanic episodes do not go to the extremes of mania (i.e. do not cause social or occupational impairment, and are without psychotic features). Bipolar II is much more difficult to diagnose, since the hypomanic episodes may simply appear as a period of successful high productivity and is reported less frequently than a distressing depression. Psychosis can occur in manic and major depressive episodes, but not in hypomania. For both disorders, there are a number of specifiers that indicate the presentation and course of the disorder, including "chronic", "rapid cycling", "catatonic" and "melancholic".

Major depressive disorder with psychotic feature (psychotic depression) is characterised in that a patient in addition to suffering from depressive symptoms also suffers from hallucinations or delusions. These patients often become paranoid and may believe that their thoughts are not their own or that others can 'hear' their thoughts.

Delusional disorders (paranoia) are a form of psychosis where the patient has long-lasting paranoid delusions which have no other physical or medical cause. These delusions may also be accompanied by auditory hallucinations.
Shared psychotic disorder (shared paranoia disorder) is a very rare condition in which people close to a mentally ill person share his or her false beliefs (delusions). As an example, a man with schizophrenia may falsely believe that his children are trying to murder him. His wife develops shared psychotic disorder and comes to believe it as well. This disorder usually occurs in long-term relationships and involves two people. However, it can also develop among members of a group, such as within families. It affects women more often than men.

Brief psychotic disorder (other and unspecified reactive psychosis) is characterised by patients who experience an acute psychotic episode lasting longer than one day but less than one month and that may or may not immediately follow an important life stress or a pregnancy (with postpartum onset). This illness usually comes as a surprise as there is no forewarning that the person is likely to break down, although this disorder is more common in people with a pre-existing personality disorder. Paranoid personality disorder is characterised by an exaggeration of the cognitive modules for sensitivity to rejection, resentfulness, distrust, as well as the inclination to distort experienced events. Neutral and friendly actions of others are often misinterpreted as being hostile or contemptuous.

Unfounded suspicions regarding the sexual loyalty of partners and loyalty in general as well as the belief that one's rights are not being recognized is stubbornly and argumentatively insisted upon. Such individuals can possess an excessive self-assurance and a tendency toward an exaggerated self-reference. Pathological jealousy, instinctive aggressive counter-attack, the need to control others, and the gathering of trivial or circumstantial "evidence" to support their jealous beliefs also features.

Schizoid personality disorder (SPD) is characterised by a lack of interest in social relationships, a tendency towards a solitary lifestyle, secretiveness, and emotional coldness. SPD is reasonably rare compared with other personality disorders, its prevalence is estimated at less than 1% of the general population. Schizotypal personality disorder, is characterized by a need for social isolation, odd behaviour and thinking, and often unconventional beliefs such as being convinced of having extra-sensory abilities. Psychosis and psychotic disorders are commonly treated with a class of medication known as atypical antipsychotics.

Anxiety disorders are a group of mental disorders characterized by feelings of anxiety and fear. Anxiety is a worry about future events and fear is a reaction to current events. These
feelings may cause physical symptoms, such as a fast heart rate and shakiness. There are a number of anxiety disorders: including generalized anxiety disorder, specific phobia, social anxiety disorder, separation anxiety disorder, agoraphobia, and panic disorder. The disorder differs by what results in the symptoms. People often have more than one anxiety disorder.

The diagnosis of anxiety disorders is difficult because there are no objective biomarkers, it is based on symptoms, which typically need to be present at least six months, be more than would be expected for the situation, and decrease functioning. Several generic anxiety questionnaires can be used to detect anxiety symptoms, such as the State-Trait Anxiety Inventory (STAI), the Generalized Anxiety Disorder 7 (GAD-7), the Beck Anxiety Inventory (BAI), the Zung Self-Rating Anxiety Scale, and the Taylor Manifest Anxiety Scale. Other questionnaires combine anxiety and depression measurement, such as the Hamilton Anxiety Rating Scale, the Hospital Anxiety and Depression Scale (HADS), the Patient Health Questionnaire (PHQ), and the Patient-Reported Outcomes Measurement Information System (PROMIS). Examples of specific anxiety questionnaires include the Liebowitz Social Anxiety Scale (LSAS), the Social Interaction Anxiety Scale (SIAS), the Social Phobia Inventory (SPIN), the Social Phobia Scale (SPS), and the Social Anxiety Questionnaire (SAQ-A30).

Agoraphobia is an anxiety disorder characterized by symptoms of anxiety in situations where the person perceives the environment to be unsafe with no easy way to get away. These situations can include open spaces, public transit, shopping malls, or simply being outside the home. Being in these situations may result in a panic attack. The symptoms occur nearly every time the situation is encountered and lasts for more than six months. Those affected will go to great lengths to avoid these situations. In severe cases people may become unable to leave their homes.

Most people who present to mental health specialists develop agoraphobia after the onset of panic disorder. Agoraphobia is best understood as an adverse behavioral outcome of repeated panic attacks and subsequent anxiety and preoccupation with these attacks that leads to an avoidance of situations where a panic attack could occur. Early treatment of panic disorder can often prevent agoraphobia. Agoraphobia is typically determined when symptoms are worse than panic disorder, but also do not meet the criteria for other anxiety disorders such as depression. In rare cases where agoraphobics do not meet the criteria used to diagnose panic disorder, the formal diagnosis of agoraphobia without history of panic disorder is used (primary agoraphobia).
Attention deficit hyperactivity disorder (ADHD) is a mental disorder of the neurodevelopmental type. It is characterized by problems paying attention, excessive activity, or difficulty controlling behavior which is not appropriate for a person's age. These symptoms begin by age six to twelve, are present for more than six months, and cause problems in at least two settings (such as school, home, or recreational activities). ADHD often persists into adulthood, with resultant impairments of social, academic and occupational functioning. In children, problems paying attention may result in poor school performance. Although it causes impairment, particularly in modern society, many children with ADHD have a good attention span for tasks they find interesting.

ADHD is diagnosed by an assessment of a person's childhood behavioral and mental development, including ruling out the effects of drugs, medications and other medical or psychiatric problems as explanations for the symptoms. It often takes into account feedback from parents and teachers with most diagnoses begun after a teacher raises concerns. It may be viewed as the extreme end of one or more continuous human traits found in all people. Whether someone responds to medications does not confirm or rule out the diagnosis. As imaging studies of the brain do not give consistent results between individuals, they are only used for research purposes and not diagnosis.

In North America, DSM-5 criteria are used for diagnosis, while European countries usually use the ICD-10. With the DSM-IV criteria a diagnosis of ADHD is 3–4 times more likely than with the ICD-10 criteria. It is classified as neurodevelopmental psychiatric disorder. Additionally, it is classified as a disruptive behavior disorder along with oppositional defiant disorder, conduct disorder, and antisocial personality disorder. A diagnosis does not imply a neurological disorder.

Premenstrual dysphoric disorder (PMDD) is a severe and disabling form of premenstrual syndrome affecting 3–8% of menstruating women. The disorder consists of a "cluster of affective, behavioral and somatic symptoms" that recur monthly during the luteal phase of the menstrual cycle. PMDD was added to the list of depressive disorders in the Diagnostic and Statistical Manual of Mental Disorders in 2013. Authoritative diagnostic criteria for PMDD are provided by a number of expert medical guides, notably the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), established seven criteria (A through G) for the diagnosis of PMDD.
Premenstrual syndrome (PMS) refers to physical and emotional symptoms that occur in the one to two weeks before a woman’s period. Symptoms often vary between women and resolve around the start of bleeding. Common symptoms include acne, tender breasts, bloating, feeling tired, irritability, and mood changes. Often symptoms are present for around six days. A woman’s pattern of symptoms may change over time. Symptoms do not occur during pregnancy or following menopause.

Huntington's disease (HD), also known as Huntington's chorea, is an inherited disorder that results in death of brain cells. The earliest symptoms are often subtle problems with mood or mental abilities. A general lack of coordination and an unsteady gait often follow. As the disease advances, uncoordinated, jerky body movements become more apparent. Physical abilities gradually worsen until coordinated movement becomes difficult and the person is unable to talk. Mental abilities generally decline into dementia. The specific symptoms vary somewhat between people. Symptoms usually begin between 30 and 50 years of age, but can start at any age. The disease may develop earlier in life in each successive generation. About 8% of cases start before the age of 20 years and typically present with symptoms more similar to Parkinson’s disease. People with HD often underestimate the degree of their problems.

Medical diagnosis of the onset of HD can be made following the appearance of physical symptoms specific to the disease. Genetic testing can be used to confirm a physical diagnosis if there is no family history of HD. Even before the onset of symptoms, genetic testing can confirm if an individual or embryo carries an expanded copy of the trinucleotide repeat in the HTT gene that causes the disease. Genetic counseling is available to provide advice and guidance throughout the testing procedure, and on the implications of a confirmed diagnosis. These implications include the impact on an individual's psychology, career, family planning decisions, relatives and relationships. Despite the availability of pre-symptomatic testing, only 5% of those at risk of inheriting HD choose to do so.

Alzheimer's disease (AD), also known as just Alzheimer's, is a chronic neurodegenerative disease that usually starts slowly and gets worse over time. It is the cause of 60% to 70% of cases of dementia. The most common early symptom is difficulty in remembering recent events (short-term memory loss). As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care, and behavioural issues. As a person's condition declines, they often
withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death. Although the speed of progression can vary, the average life expectancy following diagnosis is three to nine years.

Alzheimer's disease is usually diagnosed based on the person's medical history, history from relatives, and behavioural observations. The presence of characteristic neurological and neuropsychological features and the absence of alternative conditions is supportive.

Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. The symptoms generally come on slowly over time. Early in the disease, the most obvious are shaking, rigidity, slowness of movement, and difficulty with walking. Thinking and behavioral problems may also occur. Dementia becomes common in the advanced stages of the disease. Depression and anxiety are also common occurring in more than a third of people with PD. Other symptoms include sensory, sleep, and emotional problems. The main motor symptoms are collectively called "parkinsonism", or a "parkinsonian syndrome". A physician will diagnose Parkinson's disease from the medical history and a neurological examination.

An autoimmune disease is a condition arising from an abnormal immune response to a normal body part. There are at least 80 types of autoimmune diseases. Nearly any body part can be involved. Common symptoms include low grade fever and feeling tired. Often symptoms come and go.

There is a significant requirement for an effective treatment that is able to prevent or treat the above-discussed psychological and brain disorders without resulting in side-effects.

Summary of the invention

According to the first aspect of the present disclosure there is provided for psilocybin and/or psilocin in combination with at least one cannabinoid for use in the prevention or treatment of any of the above-discussed psychological and brain disorders, wherein the at least one cannabinoid is administered separately, sequentially or simultaneously to the psilocybin and/or psilocin.

Despite the strong prejudice against cannabis and psilocybin/psilocin, the applicant believes there is significant credible evidence supporting the use of certain cannabinoid based medicines in combination with psilocybin/psilocin.
Psilocybin is a naturally occurring psychedelic compound produced by more than 200 species of mushrooms, collectively known as psilocybin mushrooms. The most potent are members of the genus Psilocybe, such as P. azurescens, P. semilanceata, and P. cyanescens, but psilocybin has also been isolated from about a dozen other genera.

Once ingested, psilocybin is rapidly metabolized to psilocin, which then acts on serotonin receptors in the brain. The mind-altering effects of psilocybin typically last from two to six hours, although to individuals under the influence of psilocybin, the effects may seem to last much longer, since the drug can distort the perception of time. Psilocybin has a low toxicity and a relatively low harm potential, and reports of lethal doses of the drug are rare. Several modern bioanalytical methods have been adapted to rapidly and accurately screen the levels of psilocybin in mushroom samples and body fluids. Since the 1990s, there has been a renewal of scientific research into the potential medical and psychological therapeutic benefits of psilocybin for treating conditions including obsessive-compulsive disorder (OCD), cluster headaches, and anxiety related to terminal cancer.

Psilocybin is also referred to as [3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, and given the CAS number 520-52-5.

Psilocin (also known as 4-HO-DMT, psilocine, psilocyn, or psilotsin) is a substituted tryptamine alkaloid and a serotonergic psychedelic substance. It is present in most psychedelic mushrooms together with its phosphorylated counterpart psilocybin.

Psilocin also referred to as 4-hydroxy-N,N-dimethyltryptamine, and given the CAS number 520-53-6.

Cannabinoids are a group of chemicals known to activate cannabinoid receptors in cells. These chemicals, which are found in cannabis plants, are also produced endogenously in humans and other animals. These are termed endocannabinoids. Synthetic cannabinoids are chemicals with similar structures to plant's cannabinoid or endocannabinoids and it is, of course, possible to also make synthetic versions of these plant cannabinoids or endocannabinoids.
Cannabinoids possess the characteristics of being cyclic molecules exhibiting particular properties such as the ability to easily cross the blood-brain barrier, weak toxicity and few side effects.

Plant cannabinoids or phyto-cannabinoids can also be isolated such that they are "essentially pure" compounds. These isolated cannabinoids are essentially free of the other naturally occurring compounds, such as, other minor cannabinoids and molecules such as terpenes.

Essentially pure compounds have a degree of purity up to at least 95% by total weight. Some essentially pure cannabinoids (whether synthetic or isolated) have been suggested to be neuroprotective agents, either by direct antagonism of the NMDA receptor or by reducing the influx of calcium ions into the cell by another means such as binding with cannabinoid receptors.

Preferably the one or more cannabinoids are taken from the group: cannabidiol (CBD); cannabidiolic acid (CBD-A); tetrahydrocannabidiolic acid (THCVA); cannabichromene (CBC); cannabichromenic acid (CBCA); cannabigerol (CBG) and cannabigerolic acid (CBGA).

Preferably the plurality of phyto-cannabinoids are present in the form of a cannabis plant extract, which depending on the composition of the extract, may have all or a proportion of THC or THCA selectively removed.

More preferably the cannabinoid extract from at least one cannabis plant is a botanical drug substance.

Preferably the cannabinoid extract from at least one cannabis plant is produced by extraction with supercritical or subcritical C02. Alternatively the cannabinoid extract from at least one cannabis plant is produced by contacting plant material with a heated gas at a temperature which is greater than 100°C, sufficient to volatilise one or more of the cannabinoids in the plant material to form a vapour, and condensing the vapour to form an extract. Alternatively the one or more cannabinoids, including phyto-cannabinoids, may be present in a substantially pure or isolated form.
A "substantially pure" preparation of cannabinoid is defined as a preparation having a
chromatographic purity (of the desired cannabinoid) of greater than 90%, more preferably
greater than 95%, more preferably greater than 96%, more preferably greater than 97%,
more preferably greater than 98%, more preferably greater than 99% and most preferably
greater than 99.5%, as determined by area normalisation of an HPLC profile.

Preferably the substantially pure cannabinoid used in the invention is substantially free of
any other naturally occurring or synthetic cannabinoids, including cannabinoids that occur
naturally in cannabis plants. In this context "substantially free" can be taken to mean
that no cannabinoids other than the target cannabinoid are detectable by HPLC.

Substantially pure cannabinoids can be prepared from a botanical drug substance. A
technique has been established by the applicant and is described in GB2393721.

In another aspect of the present invention the cannabinoid is in a synthetic form.
References to cannabinoids, particularly with regard to therapeutic use, will be understood
to also encompass pharmaceutically acceptable salts of the cannabinoid. The term
"pharmaceutically acceptable salts" refers to salts or esters prepared from pharmaceutically
acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases
or acids, as would be well known to persons skilled in the art. Many suitable inorganic and
organic bases are known in the art.

The scope of the disclosure also extends to derivatives of cannabinoids that retain the
desired activity. Derivatives that retain substantially the same activity as the starting material,
or more preferably exhibit improved activity, may be produced according to standard
principles of medicinal chemistry, which are well known in the art. Such derivatives may
exhibit a lesser degree of activity than the starting material, so long as they retain sufficient
activity to be therapeutically effective. Derivatives may exhibit improvements in other
properties that are desirable in pharmaceutically active agents such as, for example,
 improved solubility, reduced toxicity, enhanced uptake, etc. Preferably, the cannabinoid
combined with the psilocybin/psilocin is formulated as a pharmaceutical composition further
comprising one or more pharmaceutically acceptable carriers, excipients or diluents.

The disclosure also encompasses pharmaceutical compositions comprising cannabinoids, or
pharmaceutically acceptable salts or derivatives thereof in combination with
psilocybin/psilocin, formulated into pharmaceutical dosage forms, together with suitable
pharmaceutically acceptable carriers, such as diluents, fillers, salts, buffers, stabilizers, solubilizers, etc. The dosage form may contain other pharmaceutically acceptable excipients for modifying conditions such as pH, osmolarity, taste, viscosity, sterility, lipophilicity, solubility etc. The choice of diluents, carriers or excipients will depend on the desired dosage form, which may in turn be dependent on the intended route of administration to a patient.

Suitable dosage forms include, but are not limited to, solid dosage forms, for example tablets, capsules, powders, dispersible granules, cachets and suppositories, including sustained release and delayed release formulations. Powders and tablets will generally comprise from about 5% to about 70% active ingredient. Solid carriers and excipients are generally known in the art and include, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose, etc. Tablets, powders, cachets and capsules are all suitable dosage forms for oral administration.

Suitable liquid dosage forms include solutions, suspensions and emulsions. Liquid form preparations may be administered by intravenous, intracerebral, intraperitoneal, parenteral or intramuscular injection or infusion. Sterile injectable formulations may comprise a sterile solution or suspension of the active agent in a non-toxic, pharmaceutically acceptable diluent or solvent. Liquid dosage forms also include solutions or sprays for intranasal, buccal or sublingual administration. Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be combined with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also encompassed are dosage forms for transdermal administration, including creams, lotions, aerosols and/or emulsions. These dosage forms may be included in transdermal patches of the matrix or reservoir type, which are generally known in the art.

Pharmaceutical preparations dose (for the cannabinoid and/or the psilocybin/psilocin) may be conveniently prepared in unit dosage form, according to standard procedures of pharmaceutical formulation.

The quantity of active compound(s) per unit dose may be varied according to the nature of the active compound and the intended dosage regime. Generally an effective amount shall be used, which may be within the range of from 0.01 mg to 5000 mg, preferably 0.01-4000
mg, 0.1-3000 mg, 1-2500, 5-1000, or 10-100 mg per unit dose (for the cannabinoid and/or the psilocybin/psilocin).

Generally, the weight ratio of the cannabinoids to the psilocybin/psilocin is decided by considering the properties of each constituent to be combined, the properties of drug combination and the symptoms of the patient. Preferably the weight ratio is in the range of 1 part by weight of the cannabinoid to about 0.01 to about 500 parts by weight of the psilocybin/psilocin, more preferably 1 part by weight of the cannabinoid to about 0.1 to about 100 parts by weight of the psilocybin/psilocin. More preferably the cannabinoid is a phyto-cannabinoid which may be present as a synthesized compound, an isolated compound or as an extract containing one or more other phyto-cannabinoids and other plant constituents in varying amounts. The extract may have had individual cannabinoids, such as THC, selectively removed in whole or part.

CLauses

1. Psilocybin and/or psilocin in combination with at least one cannabinoid for use in the prevention or treatment of a psychological disorder, wherein the at least one cannabinoid is administered separately, sequentially or simultaneously to the psilocybin and/or psilocin.

2. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to clause 1, wherein the psychological disorder is chosen from depression, psychotic disorder, schizophrenia, schizophreniform disorder (acute schizophrenic episode); schizoaffective disorder; bipolar I disorder (mania, manic disorder, manic-depressive psychosis); bipolar II disorder; major depressive disorder with psychotic feature (psychotic depression); delusional disorders (paranoia); Shared Psychotic Disorder (Shared paranoia disorder); Brief Psychotic disorder (Other and Unspecified Reactive Psychosis); Psychotic disorder not otherwise specified (Unspecified Psychosis); paranoid personality disorder; schizoid personality disorder; schizotypal personality disorder, anxiety disorder, panic disorder, panic attacks, agoraphobia, attention deficit syndrome, premenstrual dysphoric disorder (PMDD), and premenstrual syndrome (PMS).
3. Psilocybin and/or psilocin in combination with at least one cannabinoid for use in the prevention or treatment of a brain disorder, wherein the at least one cannabinoid is administered separately, sequentially or simultaneously to the psilocybin and/or psilocin.

4. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to clause 3, wherein the brain disorder is chosen from Huntington’s disease, Alzheimer’s disease, dementia, Parkinson’s disease.

5. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to any of the preceding clauses, wherein the at least one cannabinoid is at least one, two or three chosen from the group consisting of cannabidiol (CBD); cannabidiolic acid (CBDA); tetrahydrocannbidivar (THCV); tetrahydrocannbidivarinin acid (THCVA); cannabichromene (CBC); cannabichromenic acid (CBCA); cannabigerol (CBG) and cannabigerolic acid (CBGA).

6. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to any of the previous clauses, wherein the at least one cannabinoid is present in the form of an extract from a cannabis plant, preferably wherein the extract has all or a proportion of THC and/or THCA selectively removed.

7. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to any of the previous clauses, wherein the at least one cannabinoid is present in a composition comprising at least 2, 3, or 4 cannabinoids.

8. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to any of the previous clauses, wherein the at least one cannabinoid is present in a pure form.

9. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to any of the previous clauses, wherein the at least one cannabinoid is present in a synthetic form.

10. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to any of the previous clauses, wherein the psilocybin and/or psilocin are present in the form of an extract from a mushroom and/or truffle (sclerotium), preferably from the genus Psilocybe, Gymnopilus, Panaeolus, Copelandia, Hypholoma, Pluteus, Inocybe, Conocybe, Panaeolina, Gerronema, Agrocybe, Galerina and/or Mycena, more preferably P.
azurescens, P. semilanceata, P. cyanescens, and/or P. cubensis, P. subcubensis, P. tampanensis, P. mexicana A, P. atlantis, and/or P. semilanceata.

11. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to any of the previous clauses, wherein the psilocybin and/or psilocin are present in a pure form.

12. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to any of the previous clauses, wherein the psilocybin and/or psilocin are present in a synthetic form.

13. Psilocybin and/or psilocin in combination with at least one cannabinoid for use according to any of the previous clauses, wherein psilocybin and/or psilocin in combination with the at least one cannabinoid are comprised in a pharmaceutical composition, preferably further comprising one or more pharmaceutically acceptable carriers, excipients or diluents.

Example
In a 48-day treatment, 50 subjects suffering from diverse medical conditions receive a daily oral dose with either

- pure psilocybin (30 mg);
- pure cannabidiol (30 mg); or
- combined treatment of pure psilocybin (30 mg) + pure cannabidiol (30 mg).

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Diagnosed condition</th>
<th>Effect treatment with psilocybin</th>
<th>Effect treatment with cannabidiol</th>
<th>Effect combined treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Depression</td>
<td>6 subjects report improved mood after period of treatment</td>
<td>5 subjects report improved mood after period of treatment</td>
<td>14 subjects report improved mood after period of treatment</td>
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<tr>
<td>3</td>
<td>Psychotic disorder</td>
<td>on average, 20% increased occurrence of psychotic episodes during period of treatment</td>
<td>on average, 10% increased occurrence of psychotic episodes during period of treatment</td>
<td>on average, 70% decreased occurrence of psychotic episodes during period of treatment</td>
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<td>Schizophrenia</td>
<td>on average, 0% decreased occurrence of</td>
<td>on average, 50% decreased occurrence of</td>
<td>on average, 100% decreased occurrence of</td>
</tr>
<tr>
<td></td>
<td>Schizophrenic episodes during period of treatment</td>
<td>Schizophrenic episodes during period of treatment</td>
<td>Schizophrenic episodes during period of treatment</td>
<td></td>
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<tr>
<td>---</td>
<td>--------------------------------------------------</td>
<td>--------------------------------------------------</td>
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</tr>
<tr>
<td>4</td>
<td>Anxiety disorder on average, 50% increased occurrence of anxiety attacks during period of treatment</td>
<td>on average, 40% increased occurrence of anxiety attacks during period of treatment</td>
<td>on average, 50% decreased occurrence of anxiety attacks during period of treatment</td>
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<tr>
<td>2</td>
<td>Panic disorder on average, 50% increased occurrence of panic attacks during period of treatment</td>
<td>on average, 40% increased occurrence of panic attacks during period of treatment</td>
<td>on average, 50% decreased occurrence of panic attacks during period of treatment</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Huntington’s disease normal progression of movement, cognitive, and psychiatric disorders during treatment</td>
<td>normal progression of movement, cognitive, and psychiatric disorders during treatment</td>
<td>No progression of movement, cognitive, and psychiatric disorders during treatment</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Alzheimer’s disease normal progression of disease symptoms during treatment</td>
<td>normal progression of disease symptoms during treatment</td>
<td>No progression of disease symptoms during treatment</td>
<td></td>
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<tr>
<td>10</td>
<td>Dementia normal progression of disease symptoms during treatment</td>
<td>normal progression of disease symptoms during treatment</td>
<td>No progression of disease symptoms during treatment</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Parkinson’s disease normal progression of movement disorders during treatment</td>
<td>normal progression of movement disorders during treatment</td>
<td>No progression of movement disorders during treatment</td>
<td></td>
</tr>
</tbody>
</table>

Replacing cannabidiol with another cannabinoid may lead to similar results. Treatment according to the present disclosure leads to a decreased occurrence or decreased progression of symptoms in subjects suffering from depression, psychosis, schizophrenia, anxiety disorder, panic attacks, Huntington’s disease, Alzheimer’s disease, dementia, and/or Parkinson’s disease. No side effects were observed.
CONCLUSIES

1. Psilocybine en / of psilocine in combinatie met ten minste één cannabinoïde voor gebruik bij de preventie of behandeling van een auto-immuunziekte, waarbij de ten minste ene cannabinoïde separaat, sequentieel of gelijktijdig ten opzichte van de psilocybine en / of psilocine wordt toegediend.

2. Psilocybine en / of psilocine in combinatie met ten minste één cannabinoïde voor gebruik volgens conclusie 1, waarbij de auto-immuunziekte een hersenaandoening is gekozen uit de ziekte van Huntington, ziekte van Alzheimer, dementie, en de ziekte van Parkinson.

3. Psilocybine en / of psilocine in combinatie met ten minste één cannabinoïde voor gebruik volgens een van de voorgaande conclusies, waarbij de ten minste ene cannabinoïde ten minste één, twee of drie is gekozen uit de groep bestaande uit cannabidiol (CBD); cannabidiolisch zuur (CBDA); tetrahydrocannabidiavin (THCV); tetrahydrocannabidivariner zuur (THCVA); cannabichromene (CBC); cannabichromenic zuur (CBCA); cannabigerol (CBG) en cannabigerolic zuur (CBGA).

4. Psilocybine en / of psilocine in combinatie met ten minste één cannabinoïde voor gebruik volgens één van de voorgaande conclusies, waarbij de ten minste ene cannabinoïde in de vorm is van een extract van een cannabisplant, bij voorkeur waarbij uit het extract alle of een deel van THC en / of THCA selectief is verwijderd.

5. Psilocybine en / of psilocine in combinatie met ten minste één cannabinoïde voor gebruik volgens één van de voorgaande conclusies, waarbij de ten minste ene cannabinoïde aanwezig is in een samenstelling die ten minste 2, 3 of 4 cannabinoïden omvat.

6. Psilocybine en / of psilocine in combinatie met ten minste één cannabinoïde voor gebruik volgens één van de voorgaande conclusies, waarbij de ten minste ene cannabinoïde aanwezig is in een zuivere vorm.

7. Psilocybine en / of psilocine in combinatie met ten minste één cannabinoïde voor gebruik volgens één van de voorgaande conclusies, waarbij de ten minste ene cannabinoïde aanwezig is in een synthetische vorm.

8. Psilocybine en / of psilocine in combinatie met ten minste één cannabinoïde voor gebruik volgens één van de voorgaande conclusies, waarbij de psilocybine en / of psilocine in de vorm is van een extract van een paddestoel en / of truffel (sclerotium), bij voorkeur van het

9. Psilocybine en / of psilocine in combinatie met ten minste één cannabisöide voor gebruik volgens één van de voorgaande conclusies, waarbij de psilocybine en / of psilocine aanwezig is in een zuivere vorm.

10. Psilocybine en / of psilocine in combinatie met ten minste één cannabisöide voor gebruik volgens één van de voorgaande conclusies, waarbij de psilocybine en / of psilocine aanwezig is in een synthetische vorm.

11. Psilocybine en / of psilocine in combinatie met ten minste één cannabisöide voor gebruik volgens één van de voorgaande conclusies, waarbij psilocybine en / of psilocine in combinatie met de ten minste ene cannabisöide omvat zijn in een farmaceutisch preparaat, bij voorkeur verder omvattende één of meer farmaceutisch aanvaardbare dragers, hulpmiddelen of verdunningsmiddelen.
ABSTRACT

The present invention relates to the use of one or more cannabinoids in combination with psilocybin and/or psilocin for use in the prevention or treatment of psychological or brain disorders. Preferably the one or more cannabinoids are taken from the group cannabidiol (CBD); cannabidiolic acid (CBDA); tetrahydrocannbisavarin (THCV); tetrahydrocannbisavarinacid (THCVA); cannabichromene (CBC); cannabichromenic acid (CBCA); cannabigerol (CBG) and cannabigerolic acid (CBGA).
RAPPORT BETREFFENDE HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK

Octrooiaanvraag 2018190

<table>
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<tr>
<th>Classificatie van het onderwerp:</th>
<th>Onderzochte gebieden van de techniek:</th>
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<th>Niet onderzochte conclusies:</th>
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<td>18 januari 2017</td>
<td>-</td>
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### Van belang zijnde literatuur

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<tr>
<th>Categorie</th>
<th>Vermelding van literatuur met aanduiding, voor zover nodig, van speciaal van belang zijnde tekstgedeelten of figuren.</th>
<th>Van belang voor conclusie(s)</th>
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<tr>
<td>X</td>
<td>&quot;Cannabis and Psilocybin for Bipolar Disorder&quot;; Multidisciplinary Association for Psychedelic Studies; 7 januari 2014; [opgehaald op 19 mei 2017] <a href="http://www.maps.org/research-archive/psilo/Cannabis-and-Psilocybin-for-Bipolar-Disorder.pdf">http://www.maps.org/research-archive/psilo/Cannabis-and-Psilocybin-for-Bipolar-Disorder.pdf</a> * pagina 1, 1° alinea; pagina 3, 2° alinea *</td>
<td>1, 2, 5-13</td>
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<td>A</td>
<td>WO 2016/187277 A (KNIGHT JOSEPH ROBERT) 24 november 2016 * conclusies 2 en 11 *</td>
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Datum waarop het onderzoek werd voltooid: 19 mei 2017

De bevoegde ambtenaar: Dr. R. Boers

Octrooicentrum Nederland, onderdeel van Rijksdienst voor Ondernemend Nederland

1 Gedefinieerd volgens International Patent Classification (IPC).
2 Verklaring van de categorie-aanduiding: zie apart blad.
Categorie van de vermelde literatuur:

X: op zichzelf van bijzonder belang zijnde stand van de techniek
Y: in samenhang met andere geciteerde literatuur van bijzonder belang zijnde stand van de techniek
A: niet tot de categorie X of Y behorende van belang zijnde stand van de techniek
O: verwijzend naar niet op schrift gestelde stand van de techniek
P: literatuur gepubliceerd tussen voorrang- en indieningsdatum
T: niet tijdig gepubliceerde literatuur over theorie of principe ten grondslag liggend aan de uitvinding
E: octrooiliteratuur gepubliceerd op of na de indieningsdatum van de onderhavige aanvraje en waarvan de indieningsdatum of de voorrangdatum ligt voor de indieningsdatum van de onderhavige aanvraje.
D: in de aanvraje genoemd
L: om andere redenen vermelde literatuur
&: lid van dezelfde octrooifamilie; corresponderende literatuur
AANHANGSEL

Behorende bij het Rapport betreffende het Onderzoek naar
de Stand van de Techniek, Octrooianvraje 2018190

Het aanhangsel bevat een opgave van elders gepubliceerde octrooianvragen of octrooien (zogenaamde leden van dezelfde octroifamilie), die overeenkomen met octrooigeschriften genoemd in het rapport.
De opgave is samengesteld aan de hand van gegevens uit het computerbestand van het Europees Octrooibureau per 19 mei 2017. De juistheid en volledigheid van deze opgave wordt noch door het Europees Octrooibureau, noch door Octroicentrum Nederland gegarandeerd; de gegevens worden verstrekt voor informatiedoeleinden.

<table>
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<tr>
<th>In het rapport genoemd octrooigeschrift</th>
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<th>Overeenkomende octrooigeschriften</th>
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SCHRIFTELIJKE OPINIE

Octrooi aanvraag 2018190

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Classificatie van het onderwerp¹:
A61K 31/4045; A61K 31/352; A61P 25/00; A61K 36/07; A61K 36/062; A61K 36/185

Aanvrager:
Procare Beheer B.V.

Deze schriftelijke opinie bevat een toelichting op de volgende onderdelen:

- **[X]** Onderdeel I  Basis van de schriftelijke opinie
- **[ ]** Onderdeel II  Voorrang
- **[ ]** Onderdeel III  Vaststelling nieuwheid, inventiviteit en industriële toepasbaarheid niet mogelijk
- **[X]** Onderdeel IV  De aanvraag heeft betrekking op meer dan één uitvinding
- **[X]** Onderdeel V  Gemotiveerde verklaring ten aanzien van nieuwheid, inventiviteit en industriële toepasbaarheid
- **[ ]** Onderdeel VI  Andere geciteerde documenten
- **[ ]** Onderdeel VII  Overige gebreken
- **[X]** Onderdeel VIII  Overige opmerkingen

De bevoegde ambtenaar:
R. Boers

Octrooicentrum Nederland,
onderdeel van Rijksdienst voor Ondernemend Nederland

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¹ Gedefinieerd volgens International Patent Classification (IPC).
Schriftelijke Opinie

Onderdeel I  Basis van de schriftelijke opinie

Deze schriftelijke opinie is opgesteld op basis van de op 18 januari 2017 ingediende conclusies.

Onderdeel IV  De aanvraag heeft betrekking op meer dan één uitvinding

Vastgesteld is dat de octrooiaanvraag betrekking heeft op meer dan één uitvinding. Het onderzoek naar de stand van de techniek is beperkt tot de eerstgenoemde uitvinding in de conclusies en betreft:

☐ alle conclusies
☐ conclusie(s)

Toelichting:
Het recreatief gebruik van psilocybine en/of psilocine in combinatie met ten minste een cannabinoid, het gebruiken van “paddo’s” in combinatie met “wiet”, is algemeen bekend. D1 openbaart ook het medisch gebruik hiervan voor het verminderen van de symptomen van een bipolaire aandoening (zie onderdeel V).
Nu de combinatie van psilocybine en/of psilocine met ten minste een cannabinoid voor medisch gebruik bekend is, valt de gemeenschappelijke uitvindingsgedachte weg. Hierdoor worden de volgende uitvindingen in de onderhavige aanvraje onderscheiden:

1) psilocybine en/of psilocine in combinatie met ten minste een cannabinoid voor gebruik bij de preventie of behandeling van een psychische aandoening (conclusies 1 en 2 en de hiervan afhankelijke conclusies).

2) psilocybine en/of psilocine in combinatie met ten minste een cannabinoid voor gebruik bij de preventie of behandeling van een hersenaandoening (conclusies 3 en 4 en de hiervan afhankelijke conclusies).

Onderdeel V  Gemotiveerde verklaring ten aanzien van nieuwheid, inventiviteit en industriële toepasbaarheid

1. Verklaring

Nieuwheid
Ja: Conclusie(s) 3, 4, 6, 8, 9, 11-13
Nee: Conclusie(s) 1, 2, 5, 7, 10

Inventiviteit
Ja: Conclusie(s) 3, 4
Nee: Conclusie(s) 6, 8, 9, 11-13

Industriële toepasbaarheid
Ja: Conclusie(s) 1-13
Nee: Conclusie(s) -

2. Literatuur en toelichting
Schriftelijke Opinie

In het rapport betreffende het onderzoek naar de stand van de techniek worden de volgende publicaties genoemd:


D1 openbaart het gebruik van psilocybine en/of psilocine in combinatie met ten minste een cannabinoïde voor het verminderen van de symptomen van een bipolaire aandoening. Hierdoor wordt de materie van conclusies 1 en 2 niet nieuw bevonden. Uit D1 volgt impliciet dat een mengsel aan cannabinoïden verkregen is door het roken van cannabis, welke mengsel diverse verbindingen omvat zoals meerdere van de verbindingen die in onderhavige conclusie 5 genoemd worden. Tevens volgt uit D1 dat de psilocine door het nuttigen van paddestoelen verkregen is.

De materie van conclusies 5, 7 en 10 worden derhalve evenmin nieuw bevonden.

De conclusies 6, 8, 9, 11-13 omvatten niet meer dan gebruikelijke maatregelen binnen het vakgebied, waardoor deze conclusies niet inventief worden bevonden.

D2 is een review artikel over hallucinerende verbindingen en hun toepassing als medicijn.

D3 openbaart het gebruik van cannabis, THC of psilocine bij de behandeling van onder andere Parkinson’s of Alzheimer’s. Het document openbaart niet het gebruik van de combinatie hiervan, noch suggereert het combinaties hiervan.

Geen van de documenten openbaart of suggereert het gebruik van psilocybine en/of psilocine in combinatie met een cannabinoïde voor gebruik bij het voorkomen of behandelen van de hersenaandoeningen zoals genoemd in conclusie 4.

De materie van de tweede uitvinding zoals genoemd in conclusies 3 en 4 wordt derhalve nieuw en inventief bevonden.

Onderdeel VIII Overige opmerkingen

De volgende opmerkingen met betrekking tot de duidelijkheid van de conclusies, beschrijving, en figuren, of met betrekking tot de vraag of de conclusies naywerkbaar zijn, worden gemaakt:

Verdere voorkeuren opgenomen in conclusies 6 en 10, zijn niet beperkend voor deze conclusies.