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(54) Title: IBOGAINE FOR THE TREATMENT OF MULTIPLE SCLEROSIS

(57) Abstract: There is described a method for treating multiple sclerosis and reducing associated lesions in a patient in need thereof. The method comprises administering to the patient a therapeutically effective amount of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof.

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IBOGAINE FOR THE TREATMENT OF MULTIPLE SCLEROSIS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims the benefit under 35 U.S.C. §119(e) of provisional patent application S.N. 63/521,530, filed June 16, 2023, the contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0002] In one of its aspects the present invention relates to the treatment of multiple sclerosis in a subject. In another of its aspects, the present invention relates to a pharmaceutical composition useful for treatment of multiple sclerosis in a subject. In yet another of its aspects, the present invention relates to a pharmaceutical composition useful for treatment of multiple sclerosis while reducing associated lesions in a subject.

DESCRIPTION OF THE PRIOR ART

[0003] Multiple sclerosis (MS) is generally known as an autoimmune disease of the central nervous system with both autoimmune and neurodegenerative features. It affects approximately 400,000 persons in the United States and 1.2 million persons worldwide. It is a major cause of neurological disability in young adults, who usually present with a relapsing, remitting pattern of neurologic involvement and progress to a chronic phase with increasing difficulty in ambulation and coordination.

[0004] Studies have shown that nearly fifty percent of MS patients require an assistive device to walk after a decade of disease. Therefore, the societal impacts of both direct medical and indirect economic costs of MS are enormous and often imposed on young families.

[0005] Currently used drugs/agents for MS treatment either modify or suppress the body's immune system. They have been shown to modestly reduce neurological relapses of the disease and, in some instances, incompletely slow the progression of neurological disability.

[0006] In addition, drugs/agents for MS treatment have not been reported to reduce the lesions associated with MS.

[0007] However, the vast majority of currently used drugs/agents for MS are variously limited by incomplete efficacy, side effects and medical risks – e.g., injection site reactions, including skin necrosis; flu-like symptoms; depression; psychosis; hypersensitivity; allergic reactions; cardiac and other organ toxicity from diabetes mellitus; cataracts; bone necrosis; serious and life threatening opportunistic infections, and risk of malignancy. The existence of these side effects and risks precludes the use of these drugs in many MS patients.

[0008] Thus, there is a pressing need for therapeutic approaches/agents that are safe, efficacious, well- tolerated, and which can be administered more conveniently. Ideally, such a therapeutice approach/agent would also concurrently reduce lesions in the patient that are associated with multiple sclerosis.

SUMMARY OF THE INVENTION

[0009] It is an object of the present invention to obviate or mitigate at least one of the above-mentioned disadvantages of the prior art.

[0010] It is another object of the present invention to provide a novel method for treating multiple sclerosis.

[0011] Accordingly, in one of its aspects, the present invention provides a method for treating multiple sclerosis and reducing associated lesions in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof.

[0012] Thus, it has been surprisingly discovered that ibogaine can be use to concurrently treat multiple sclerosis and reduce its associated lesions in a patient.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0013] Various terms used throughout this specification are intended to have the following meanings.

[0014] By "ameliorate" is meant decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease.

[0015] By "analog" is meant a molecule that is not identical, but has analogous functional or structural features. For example, an ibogaine analog retains the biological activity of ibogaine, while having certain modifications that enhance the analog's function relative to the reference compound. Such modifications could increase the analog's oral availability, or half-life.

[0016] In this specfication, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean " includes," "including," and the like; "consisting essentially of or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

[0017] By "effective amount" is meant the amount of a required to ameliorate the symptoms of a disease relative to an untreated patient. The effective amount of active compound(s) used to practice the present invention for therapeutic treatment of a disease varies depending upon the manner of administration, the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen. Such amount is referred to as an "effective" amount.

[0018] By "disease" is meant any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ. Examples of diseases include multiple sclerosis.

[0019] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50.

[0020] As used herein, the terms "treat," treating," "treatment," and the like refer to reducing or ameliorating a disorder and/or symptoms associated therewith. It will be appreciated that,

although not precluded, treating a disorder or condition does not require that the disorder, condition or symptoms associated therewith be completely eliminated.

[0021] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. Unless specifically stated or obvious from context, as used herein, the terms "a", "an", and "the" are understood to be singular or plural.

[0022] Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1 %, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein are modified by the term about.

Methods of Use

[0023] The present invention provides methods of treating multiple sclerosis and related diseases and/or disorders or symptoms thereof which comprise administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of the formulae (e.g., ibogaine and ibogaine analogs) herein to a subject (e.g., a mammal such as a human). Thus, one embodiment is a method of treating a subject suffering from or susceptible to multiple sclerosis disease or symptoms thereof. The method includes the step of administering to the mammal a therapeutic amount of an amount of ibogaine or an ibogaine analog sufficient to treat the disease or disorder or symptom thereof, under conditions such that the disease or disorder is treated.

[0024] The methods herein include administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect.

[0025] Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method).

[0026] The therapeutic methods of the invention (which include prophylactic treatment) in general comprise administration of a therapeutically effective amount of the compounds herein, such as a compound of the formulae herein to a subject (e.g., animal, human) in need

thereof, including a mammal, particularly a human. Such treatment will be suitably administered to subjects, particularly humans, suffering from, having, susceptible to, or at risk for a disease, disorder, or symptom thereof.

[0027] Determination of those subjects "at risk" can be made by any objective or subjective determination by a diagnostic test or opinion of a subject or health care provider (e.g., genetic test, enzyme or protein marker, Marker (as defined herein), family history, and the like).

[0028] In one embodiment, the invention provides a method of monitoring treatment progress. The method includes the step of determining a level of diagnostic marker (Marker) (e.g., any target delineated herein modulated by a compound herein, a protein or indicator thereof, etc.) or diagnostic measurement (e.g., screen, assay) in a subject suffering from or susceptible to a disorder or symptoms thereof associated with multiple sclerosis, in which the subject has been administered a therapeutic amount of a compound herein sufficient to treat the disease or symptoms thereof. The level of Marker determined in the method can be compared to known levels of Marker in either healthy normal controls or in other afflicted patients to establish the subject's disease status.

[0029] In preferred embodiments, a second level of Marker in the subject is determined at a time point later than the determination of the first level, and the two levels are compared to monitor the course of disease or the efficacy of the therapy. In certain preferred embodiments, a pre-treatment level of Marker in the subject is determined prior to beginning treatment according to this invention; this pre-treatment level of Marker can then be compared to the level of Marker in the subject after the treatment commences, to determine the efficacy of the treatment.

[0030] The invention further relates to methods for treatment and/or prevention of multiple sclerosis, including symptoms associated with multiple sclerosis, and/or other disease/disorder affecting the nervous system (e.g. central, peripheral) or muscle including symptoms thereof, in a subject in need thereof using the compounds and compositions described herein.

[0031] Subject within the scope of the present invention is a mammal, such as a human or a veterinary animal, exhibiting symptoms and/or suffering from, or diagnosed with, diseases/disorders described herein. The term "veterinary animal" refers to any animal cared

for, or attended to by, a veterinarian, and includes companion (pet) animals and livestock animals, for example, a cat, a dog, and a horse (e.g., a race horse). Other mammals, e.g., such as those used as experimental models for MS, mice, rats, rabbits, nonhuman primates, such as monkeys, are also within the scope of the invention (e.g. experimental allergic encephalomyelitis (EAE)).

[0032] Herein, "multiple sclerosis" is used as per the accepted textbook definition in the field (Handbook of Multiple Sclerosis. 3rd Edition. Edited by Stuart D. Cook. Marcel Dekker, Inc., 2001). Diagnostic criteria used to identify a subject with multiple sclerosis would be apparent to a person of skill in the art. For example, a skilled individual would appreciate that clinically defined multiple sclerosis is based on two attacks of neurological dysfunction separated in time and space. More recent diagnostic criteria for MS include the presence of characteristic areas on cranial or cervical magnetic resonance imaging (MRI).

[0033] Multiple sclerosis frequently begins in young adulthood with episodic attacks of neurological dysfunction – e.g., visual loss, sensory alterations, motor weakness, ataxia, etc. These subjects are within the scope of the present invention. Although the precise cause of multiple sclerosis is largely unknown, it is thought to result from an autoimmune reaction to the protein component of the myelin that forms a sheath-like covering around nerve axons and enhances electrochemical signaling in the central nervous system. Examples of such protein components include, but are not limited to, myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein.

[0034] Common symptoms of multiple sclerosis and other diseases/disorders affecting nerves and muscles include, but are not limited to, weakness, muscle stiffness, pain, which can be burning, throbbing, aching, imbalance, asthenia or fatigue, depression, visual disturbances or loss, headache, loss of bowel or bladder control, ataxia of gait or limb movements, difficulty walking, difficulty with coordinated movements of the upper extremities, cognitive dysfunction, loss or aberrant sensation, muscle cramps or spasms, among others. Subjects exhibiting these symptoms are within the scope of the present invention.

[0035] Certain known subtypes of multiple sclerosis exist that are generally defined by the profile of symptoms exhibited by the subject, including onset, duration, and patterns of

neurological dysfunction and/or disability. Subjects suffering from MS subtypes are also within the scope of the invention.

[0036] Relapses of multiple sclerosis are discrete occurrences of a subtype of multiple sclerosis known as relapsing remitting multiple sclerosis (RRMS) and occur less often in secondary progressive multiple sclerosis (SPMS). As used herein, a "relapse" is defined as the onset of new or worsening neurological symptoms usually lasting at least 48 hours in the absence of any precipitating factor, such as fever orinfection. Subjects suffering from relapses or RRMS are within the scope of the present invention.

[0037] Relapses of multiple sclerosis, include but are not limited to, symptoms which may occur alone or in combination of increased or new onset numbness in the trunk or limbs, weakness of the trunk or limbs, imbalance, difficulty walking, reduced or double vision, pain of the face, trunk or extremities, difficulty in urination or bowel movements, sexual dysfunction, cognitive difficulties such as confusion, depression, psychosis or memory loss, vertigo or dizziness, fatigue, and cramps or spasms.

[0038] Subject exhibiting these symptoms are within the scope of the present invention.

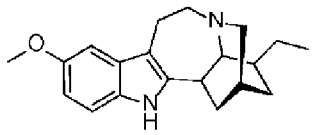
[0039] The goal of treatment of relapses is to stop the autoimmune process associated with the relapse and/or to prevent or minimize residual neurological damage associated with incomplete remission, which occurs in a high percentage of patients. There is a significant risk of permanent and severely disabling neurological disability over time, particularly if the disease enters a chronic progressive phase after a relapsing remitting phase (CPMS). Ten percent of patients never experience a relapsing phase prior to a progressive phase and this is termed primary progressive multiple sclerosis (PPMS). There is also a risk that untreated or uncontrolled relapses lead to a state of SPMS, in which progressive neurological disability, including dementia, chronic vertigo, fatigue, visual impairment, motor weakness, sensory disturbances, bladder and bowel dysfunction, ambulation difficulties or non- ambulation, ataxia and pain occur in the absence or reduced frequency of discrete attacks. SPMS and PPMS respond poorly to current drug treatment. Subjects with CPMS and PPMS are also within the scope of the invention.

Ibogaine

[0040] Ibogaine has been used as a botanical preparation from the root bark of iboga tabernathe for over 100 years both as a crude preparation, as isolated ibogaine, which was marketed in France until about 1970, or more recently as semi-synthetic ibogaine that can be produced from voacangine or other similar alkaloids. The therapeutic use of ibogaine is limited due to potentially adverse side effects. For example, in larger dosages ibogaine exhibits stimulant and hallucinogenic properties, and in addition, can induce temporary ataxia and tremors. At conventional doses, ibogaine causes these side effects in a majority of patients receiving treatment.

[0041] In the United States, ibogaine is classified as a Schedule I controlled substance. The use of ibogaine in humans is complicated by the fact that the ranges in the prior art are exceptionally broad (0.01 to 1000 mg/kg body weight). Furthermore, the ranges generally used to treat addiction (e.g., 15 mg/kg to 20 mg/kg) cause hallucinations and may be fatal. Lotsof and Wachtel, Manual for Ibogaine Therapy: Screening, Safety, Monitoring & Aftercare (2d revision, 2003), accessed at www.ibogaine.desk.nl/manual.html; Hoelen, et al. New Engl. J. Med. 360(3), 308 (2009), which is incorporated herein by reference in its entirety for all of its methods, compositions and teachings. See also the Clinical Guidelines for Ibogaine Assisted Detoxification: https://ibogaineguidelines.com.

[0042] "Ibogaine" refers to the compound:



It should be understood that where "ibogaine" is mentioned herein, one more polymorphs of ibogaine can be utilized and are contemplated. Ibogaine is isolated from Tabernanth iboga, a shrub of West Africa. Ibogaine can also be synthesized using known methods. See, e.g., Buchi, et al. (1966), *J. Am. Chem Society*, 88(13), 3099-3109 Unless specified otherwise, "ibogaine" as used herein refers to ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof. It may also refer to an ibogaine mixture, such as a botanical extraction of Taberntanthe iboga, or other alkaloids found present in it, including ibogamine, ibogaline, tabernanthine, coronoradine, voacangine, etc.

Treatment Methods

[0043] In a preferred embodiment, the treatment comprises an initial flood dose of ibogaine followed by a daily microdose for a number of days after the initial flood dose.

[0044] In a preferred embodiment, the initial flood dose of ibogaine is selected from a dosing range (adjusted by patient body weight) of from about 3 to about 24 mg/kg, from about 5 to about 21 mg/kg, preferably from about 8 to about 18 mg/kg, preferably from about 10 to about 15 mg/kg, preferably from about 12 to about 14 mg/kg.

[0045] At 13mg/kg, to is preferred toan upper limit of 1200 mg total for the initial calculated flood dosage.

[0046] In some cases, one or more booster dosages of 100-600 mg (typically 200-400 mg) can be provided 12 hours or more before or after the flood in order to boost levels of noribogaine. This can be preferable in cases where the patient either felt less effect than desired from the medicine, or where dosing was interrupted for tolerability.

[0047] By combining these methods, in some cases the equivalent or greater than a single flood dose over a period of time can be provided for patients with high sensitivity or tolerability issues, and achieve similar or greater saturation of noribogaine.

[0048] In a preferred embodiment, the microdose of ibogaine is selected from a dosing range of from about 8 to about 300 mg, from about 10 to about 200 mg, preferably from about 12 to about 150 mg, preferably from about 15 to about 80 mg, preferably from about 20 to about 60 mg.

[0049] In a preferred embodiment powdered ibogaine hydrochloride is compounded to the appropriate ratio with vitamins. In a preferred embodiment, a sodium ascorbate or calcium ascorbate form of Vitamin C is included in the composition. Preferably, capsules are filled with the mixture in bulk and bottled.

Dosing Instructions

[0050] Microdosing preferably begins from 1-14 days, more preferably 1-3 days, after a flood dose in order to benefit from and boost noribogaine saturation.

[0051] Microdosing can be maintained for psychotherapeutic effect, and for increased exposure to ibogaine and noribogaine and resulting benefit to lesion reduction over time. Patients can be coached that after 1-2 months they can choose to take breaks in the daily schedule of microdosing, including stopping dosages for 1-4, or 2-3 weeks in order to reduce any accumulation of tolerance to the medicine and also to self-evaluate their current status in regards to physican and mental symptoms. In these instances, patients are requested to keep a diary of dosage days for case studies.

[0052] Any changes to medication or health status may be discussed with the clinic physician.

[0053] Patients are directed to take one capsule daily in the morning. In cases where effects drop off or are not noticeable after 2 weeks, dosages can be tapered upward.

[0054] Patients are coached regarding potential tolerability, most of which are dose dependent. Dosing late in the day, and especially at night, can lead to sleep disturbances. Higher sensitivity to caffeine and other drugs can be noted. Medication contraindications should be closely monitored. Dosages that have more than the most mild psychoactive properties are typically unwanted for daily dosing.

[0055] Embodiments of the invention will be illustrated with reference to the following non-limiting Examples which should not be use to construe or limit the scope of the invention.

EXAMPLE 1

Patient A ("A")

[0056] In August, 2022, an Ambio Life Sciences ("Ambio") facility in Tijuana, Mexico admitted a 44-year-old man seeking ibogaine treatment related to diagnoses of post-traumatic stress disorder (PTSD), major depressive disorder (MDD), and a traumatic brain injury (TBI) that occurred in 2013. In addition, A reported periodic vertigo sensations, which he believed to be associated with high levels of alcohol consumption.

[0057] Following the treatment, the patient refrained from the use of alcohol, and vertigo resolved for a two-month period. Upon relapse he underwent further testing and was diagnosed with Relapsing Remitting Multiple Sclerosis (RRMS). He had been prescribed

dimethyl fumarate and Vitamin D to help control relapse of symptoms, but he returned for treatment at Ambio in February, 2023, at which time he was experiencing progressive alterations in mobility and coordination of fine motor movements, nocturnal vertigo, as well as bradypsychia and alterations in short-term memory. Emotional stress from relationship dissatisfaction and a potential divorce was a strong additional factor in the patient's intent for treatment.

Patient B ("B")

[0058] Also in February, 2023, a 44-year-old woman contacted Ambio inquiring about ibogaine treatment. She had previously been diagnosed with Complex Post Traumatic Stress Disorder (CPTSD) related to childhood trauma. In addition, she had a family history of MS, and was diagnosed with Secondary Progressive Multiple Sclerosis (SPMS) in 2019. Since that time she had experienced progressing alterations in mobility and coordination of fine movements, an increase of pain and muscle rigidity, as well as depression, anxiety and fatigue.

[0059] Following the insertion of a subdermal baclophen pump she had substantial ambulatory disability. At intake she displayed a high level of muscle rigidity, her extremities and upper limbs were hypotrophic, and she required the use of a wheelchair as well as transfer assistance. Before seeking out ibogaine treatment, B had exhausted other treatment options. She was continuing to use baclophen to manage pain despite the resulting reduction in mobility, as well as high doses of medical cannabis. These treatments helped to manage certain symptoms, but rigidity had progressed to the point that she was unable to participate in physiotherapy.

Methodology

[0060] The treatment that was conducted in each case included an exposure to a higher dosage (A: 1200mg, and B: 450mg) of ibogaine hydrochloride during an inpatient stay at an Ambio facility, followed by subsequent microdoses of 20 mg per day. The ibogaine used in treatment is produced semi-synthetically via voacangine that is extracted from Voacanga africana. Independent TLC analysis showed no impurities.

[0061] Neither Patient A nor Patient B took breaks from daily microdosing during the observations periods described.

Preparation and dosing

[0062] Powdered ibogaine hydrochloride was administered in capsule form and divided into 3 to 5 (A: 4, B: 3) additional dosages. An initial test dose of 200-600 mg/kg (typically 400mg) is administered, followed by equal divisions of the remainder beginning after 30-90 minutes, and continuing then at 15-30 minute intervals. The intent is to ingest the complete initially calculated dose within an initial 2 hour window.

Adjustments for tolerability

[0063] Some patients are unable/unwilling to ingest the last measured dosage, or are so overwhelmed by the effects that it is deemed unnecessary by the facilitator.

[0064] Some patients feel little effect from the initial calculated dosage even after 3 hours or more. Between 2.5-3 hours we sometimes discuss a booster dosage for those who feel comfortable a stronger effect. This additional dosage can range from 2-5 mg/kg. It is sometimes preferred when we select the upper limit dosing of 1200 mg. This dose is additional to the initial calculated dose, raising the overall dosage by weight.

Further optional adjustments

[0065] In some cases, one or more test dosages of 200-600 mg (typically 400 mg) can be provided in advance of the flood dose by 8 hours or more. This can be preferable in cases of individuals who present as highly sensitive, emotionally or physically, in order to observe tolerability more carefully. This kind of dosing was provided to Patient B.

Evaluation

[0066] Patients were evaluated with electrocardiograms, blood work and an 18-panel urine drug screen. They were under constant cardiac monitoring for a minimum of 12 hours during high dose events, and were administered a metabolic assistance protocol that includes medications and IV therapies.

[0067] Patient A was also evaluated with a pre- and post-treatment MRI, which were assessed. Both patients were evaluated by a psychologist and a medical doctor. Psychological assessment included a semi-structured interview about the subjective effects of ibogaine, as well as the complete Multiple Sclerosis Quality of Life Inventory (MSQLI), questions on which cover a 4-week period, which was collected at baseline ("BL"), and at one ("1M") and two month ("2M") follow-ups. Medical evaluation included Functional Scale, the Ambulatory Index, and the Expanded Disability Status Scale, which measure physical disability, and which were collected at baseline and at a two month follow-up.

Observations

Imaging Results

[0068] The MRI images for Patient A demonstrate a marked reduction of all demyelination. This is believed to be a significant finding, to the knowledge of the inventor, as no existing treatment for MS is has been shown to reduce lesions.

Quantitative Results

[0069] Quantitative measures that were collected corroborate imaging findings, and demonstrate a corresponding improvement in symptoms. With minimal exceptions, both patients reported substantial improvements across all measures at one month that were either sustained or further improved at two months.

[0070] Patient A had the most substantial reduction around MSQLI scores for Fatigue Impact (MFIS) (BL: 52, 1M: 29, 2M: 4). At 2M he described an essential elimination of fatigue symptoms and the effect of fatigue on QOL. The same patient had a complete resolution of minor reported bladder control issues from baseline (BL: 4, 1M: 0, 2M: 0).

[0071] Patient B's most substantial reduction was registered by the MSQLI Pain Experience Scale (PES) (BL: 22, 1M: 8, 2M: 6). Also notable were reductions of scores for the Ambulatory Index (BL: 8, 1M: 7, 2M: 6) that describe general mobility. These results were attributed in large part to the relaxation of intense muscle rigidity. She also noted substantial improvements in scores for bladder (BL: 5, 1M: 3, 2M: 3) and bowel control (BL: 6, 1M: 5, 2M: 2).

[0072] The MSQLI measures mental health in several ways, firstly as an impact mental/emotional experience on overall health and daily function (MF-36-MH), second on a measure for Perceived Deficits (PDQ), and third as an overall mental health score (MHI). There were improvements in all of these measures between BL and 2M, but changes across these three measures were not always directly correlated with each other. MF-36-MH scores seemed to either plateau or peak at 1M (A: BL: 31.6, 1M: 54.7, 2M: 54.6; BL: 36.3, 1M: 54.5, 2M: 46.5). PDQ scores saw the most consistent and linear improvements in both patients (A: BL: 42, 1M: 40, 2M: 33; B: BL: 40, 1M: 30, 2M: 25). MHI scores improved by 38-39% from baseline to 2M in both patients, but in inconsistent ways (A: BL: 41.7, 1M: 59.6, 2M: 57.8; B: BL: 22.7, 1M: 19.5, 2M: 31.3), showing a plateau in Patient A equivalent to PDQ scores, and a dip at 1M, followed by a sharp increase at 2M in Patient B. The mean overall improvement amongst mental health scores in both patients was 44.2%.

[0073] Amongst the 3 scales used to measure physical disability, the Ambulatory index was negligible for Patient A who had no issue with ambulation. The mean improvement on other disability scores for Patient A was 71.5%, and 30% for Patient B.

EXAMPLE 2

[0074] In the Example, gait recovery and spinal cord damage repair are assessed using the model described in Fiander et al., *Behavioural Brain Research*, 317 (2017) 95-108. See also Chedrawe et al., *Journal of Neuroimmunology*, 321 (2018) 72-82.

Gait Recovery

[0075] The effect of both a vehicle and ibogaine gait recovery following a mouse model of MS is assessed.

[0076] More specifically, gait recovery is assessed after adminstration of an ibogaine formulation comprising ibogaine and a vehicle. A control is established by assessing gait recovery after adminstration of the vehicle only.

[0077] Kinetic gait analysis is performed before administration (day -2) and after administration (day 7, 14, 21, 28, 35, and 42) using modeled brain inflammation and demyelination. Experimental autoimmune encephalomyelitis (EAE) is induced by injecting myelin oligodendrocyte glycoprotein (MOG) or proteolipid protein (PLP). To assess the

ability of ibogaine to reverse gait deficits, vehicle only (NEOBEE; 100 µl) or ibogaine formulation (40 mg/kg) is administered orally after the gait measuresments at day 7.

[0078] Statistical comparisons between the vehicle only and ibogaine formulation treated animals is performed using a two-way repeated measured ANOVA followed Sidak's multiple comparison tests for gait data from days 14, 21, 28, 35, and 42.

Spinal Cord Damage Repair

[0079] After the gait measurements on day 42, spinal cord injury and metabolic enzyme, mitochondrial, and neurotrophin, and myelin-related gene expression is quantified in the spinal cord. Using LC-MS-MS, ibogaine and noribogaine levels in the plasma and cortex are measured in subgroups of EAE mice 1, 4, and 24 hours after oral dosage with the ibogaine formulation.

[0080] mRNA levels for phosphoglycerate kinase, malonate dehydrogenase, aldolase A, enolase, glyceraldehyde-3-phosphate dehydrogenase, pyruvate kinase, copper-zinc superoxide dismutase, Complex I-V subunits, and myelin-related genes (MOG, MAG, and PLP2) are measured in the spinal cord using reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Histology is performed using eriochrome cyanine staining to detect myelin and immunohistochemistry to label oligodendrocyte progenitor cells, oligodendrocytes, neurons, and axons in spinal cords harvested from additional mice. Computer assisted image analysis is then used to quantify these markers. Statistical analysis is performed using the Mann Whitney U test. Power analysis indicates that 6 mice/group will detect a predicted 50% difference between means with a standard deviation of 15% with 100% accuracy at alpha=0.05.

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[0081] While this invention has been described with reference to illustrative embodiments and examples, the description is not intended to be construed in a limiting sense. Thus, various modifications of the illustrative embodiments, as well as other embodiments of the invention, will be apparent to persons skilled in the art upon reference to this description. It is therefore contemplated that the appended claims will cover any such modifications or embodiments.

[0082] All publications, patents and patent applications referred to herein are incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

What is claimed is:

1. A method for treating multiple sclerosis and reducing associated lesions in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof.

2. The method defined in Claim 1, wherein the treatment comprises an intial flood dose of ibogaine followed by a number of microdoses of ibogaine.

3. The method defined in Claim 2, wherein the initial flood dose of ibogaine is selected from a dosing range (adjusted by patient body weight) of from about 3 to about 24 mg/kg.

4. The method defined in Claim 2, wherein the initial flood dose of ibogaine is selected from a dosing range (adjusted by patient body weight) of from about 5 to about 21 mg/kg.

5. The method defined in Claim 2, wherein the initial flood dose of ibogaine is selected from a dosing range (adjusted by patient body weight) of from about 8 to about 18 mg/kg.

6. The method defined in Claim 2, wherein the initial flood dose of ibogaine is selected from a dosing range (adjusted by patient body weight) of from about 10 to about 15 mg/kg.

7. The method defined in Claim 2, wherein the initial flood dose of ibogaine is selected from a dosing range (adjusted by patient body weight) of from about 12 to about 14 mg/kg.

8. The method defined in any one of Claims 2-7, wherein the initial flood dose of ibgaine does not exceed 1200 mg.

9. The method defined in any one of Claims 2-8, wherein the microdose of ibogaine is selected from a dosing range of from about 8 to about 300 mg.

10. The method defined in any one of Claims 2-8, wherein the microdose of ibogaine is selected from a dosing range of from about 10 to about 200 mg.

11. The method defined in any one of Claims 2-8, wherein the microdose of ibogaine is selected from a dosing range of from about 12 to about 150 mg.

12. The method defined in any one of Claims 2-8, wherein the microdose of ibogaine is selected from a dosing range of from about 15 to about 80 mg.

13. The method defined in any one of Claims 2-8, wherein the microdose of ibogaine is selected from a dosing range of from about 20 to about 60 mg.

14. The method defined in any one of Claims 2-13, wherein the micodose of ibogaine is administered daily.

15. The method defined in any one of Claims 2-14, wherein the microdose of ibogaine is administered for a duration of from about 1 to about 4 weeks.

16. The method defined in any one of Claims 2-14, wherein the microdose of ibogaine is administered for a duration of from about 2 to about 3 weeks.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2024/050807

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/55*** (2006.01), ***A61P 21/00*** (2006.01), ***A61P 25/28*** (2006.01), ***C07D 487/22*** (2006.01)

CPC: **A61K 31/55** (2020.01), A61K2121/00 (2020.01), A61P 21/00 (2020.01), A61P 25/28 (2020.01), C07D 487/22 (2020.01)

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)
IPC: A61K 31/55 (2006.01) , A61P 21/00 (2006.01) , A61P 25/28 (2006.01) , C07D 487/22 (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Intellect, Questel Orbit, STN, Google Scholar, Scopus, Google

Keywords: Ibogaine and multiple sclerosis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	US 2023/0059204 A1 (PLAKOGIANNIS et al.) 23 February 2023 (23-02-2023) *see whole document	1-16
X, Y	AMBIO, "*Personal Change*". 1 February 2023 (01-02-2023),, [online] [retrieved on 31 July 2024 (31-07-2024)]. Retrieved from the Internet: <https://web.archive.org/web/20230201160227/https:/ambio.life/personal-change/#regeneration> *see section "Regeneration"	1-16
Y	KARADIMOV, D., TSONCHEV, Z., "*Neuroprotection*". Anaesthesiology and Intensive Care, 2007, Vol. 34(4), pp. 30-36, [online]. *see whole document **a machine translation of the document was used	1-16

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"D"	document cited by the applicant in the international application	"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
"E"	earlier application or patent but published on or after the international filing date	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search	Date of mailing of the international search report 30 August 2024 (30-08-2024)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Andrew Williams 819-664-0084

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 3113771 A1 (MAILLET et al.) 11 January 2017 (11-01-2017) *see whole document	1-16

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2024/050807

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US2023059204A1	23 February 2023 (23-02-2023)	WO2023012691A1	09 February 2023 (09-02-2023)