Abstract:
A method of treating addiction to drugs of abuse, comprising administering to a subject a pharmaceutical composition comprising (a) ibogaine, a ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof, and (b) an agent inert to the pharmaceutical composition.

International Classification:
A61K 31/404 (2006.01) A61P 25/30 (2006.01)
A61K 31/55 (2006.01) A61P 25/34 (2006.01)
A61K 31/4738 (2006.01)

Applicant:
DEMERX, INC., Florida (US).

Inventors:
MAILLET, Emeline; c/o DEMERX, INC., 305 South Andrews Avenue, Suite 515, Fort Lauderdale, Florida 33301 (US).
FRIEDHOFF, Lawrence; c/o DEMERX, INC., 305 South Andrews Avenue, Suite 515, Fort Lauderdale, Florida 33301 (US).

Priority Data:
61/987,397  3 March 2014 (03.03.2014) US
61/982,724  13 March 2014 (13.03.2014) US
61/982,718  13 March 2014 (13.03.2014) US
61/982,743  13 March 2014 (13.03.2014) US
61/952,736  13 March 2014 (13.03.2014) US
61/952,740  13 March 2014 (13.03.2014) US
61/952,725  13 March 2014 (13.03.2014) US
62/049,968  12 September 2014 (12.09.2014) US


Declarations under Rule 4.17:
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(m))

Published:
— with international search report (Art. 21(3))
THERAPEUTIC USES OF IBOGAINE AND RELATED COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS


FIELD OF THE INVENTION

[0002] This invention relates generally to the use of each of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof at a dosage that provides a therapeutic serum concentration for treating or preventing a disease or disorder in a patient.

STATE OF THE ART

Nicotine Addiction

[0003] Nicotine addiction relates generally to smoking, although other forms of nicotine addiction are common (e.g., chewing tobacco). Smoking and other forms of nicotine use pose a serious threat to global health. In the United States alone, annual mortality from smoking (including environmental exposure, i.e. "second-hand smoke") is greater than 440,000. Costs associated with smoking-related illness in the United States total $96 billion in medical costs and $97 billion in lost productivity each year. Furthermore, smoking significantly increases the risk of a number of diseases, including coronary artery disease, stroke, lung cancer and other cancers, and chronic obstructive pulmonary disease. An estimated 46 million people in the United States are smokers, 20.6 percent of the US population.

[0004] More than 40 percent of existing smokers attempt to quit smoking annually. Various approved therapies (varenicline, bupropion, nicotine patch/gum, nicotine nasal spray/inhaler, hypnotherapy, biofeedback) have long been in clinical use to treat nicotine dependence.
Current therapies directed toward smoking cessation tend to focus on counseling, behavioral treatment such as hypnosis, and/or pharmaceutical therapies. Quitting smoking is difficult and may require multiple attempts, with success rates of 4% to 25% depending on the technique used. Users often relapse because of stress, weight gain, and withdrawal symptoms. Furthermore, nicotine replacement therapies (e.g., nicotine patch, nicotine gum, nicotine nasal spray, or nicotine inhaler) do not directly treat nicotine addiction, as the patient remains addicted to nicotine throughout treatment.

A nicotine addict in remission may exhibit psychological symptoms of nicotine addiction long after the physical symptoms of nicotine addiction are gone. Many ex-smokers relapse due to a trigger, such as stress or environmental cues. For example, approximately 50% of relapses occur when the ex-smoker has been drinking alcohol.

Alcohol Dependence

Alcohol dependence (also referred to alcohol abuse, alcohol addiction, or alcoholism) is a serious public health problem throughout the world. As many as 140 million people worldwide have an alcohol abuse problem, although only a small fraction of those receive treatment. Alcohol abuse can cause damage to almost every organ in the body, including the brain. Long-term alcohol abuse is known to cause or contribute to numerous diseases, including cirrhosis of the liver, pancreatitis, epilepsy, dementia, heart disease, peptic ulcers, damage to the central and/or peripheral nervous system, cancer, polyneuropathy, nutritional deficiencies, and death.

Complicating the treatment of alcohol dependence, alcohol-dependent patients generally experience significant, potentially fatal, withdrawal symptoms while attempting to quit using alcohol. Acute withdrawal lasts one to three weeks after cessation of alcohol consumption. Acute withdrawal symptoms include anxiety, seizures, delirium tremens (DTs), hallucinations, shakes, and heart failure. Post-acute withdrawal can last significantly longer, with symptoms such as anxiety, depression, sleep disturbance, fatigue, and tension being common.

Treatment for alcohol dependence generally includes detoxification followed by individual and/or group therapy. Detoxification may include treatment with medications (such as benzodiazepines) that reduce the symptoms of withdrawal. However, drugs such as benzodiazepines have numerous negative side effects, including adverse psychological
effects and physical dependence. Benzodiazepines are also known to increase alcohol cravings in alcohol dependent people, and are thus not suitable for long-term treatment of alcohol dependence/addiction.

**Substance or Drug Addiction**

[0009] Substance or drug addiction is a serious public health problem throughout the world. Heroin and other opioids, including prescription painkillers, are widely abused and account for a large percentage of illicit drug use. Opioid use is also linked to approximately 50% of violent crimes in the United States and costs the U.S. economy billions of dollars per year. As many as 23.5 million people in the US (almost 10%) have a drug or alcohol abuse problem, although only a small fraction of those receive treatment.

[0010] Complicating the treatment of drug addiction, drug-addicted patients generally experience significant withdrawal symptoms while attempting to quit using the drug. Acute withdrawal from drug dependence is characterized by dramatic and traumatic symptoms, including sweating, racing heart, palpitations, muscle tension, tightness in the chest, difficulty breathing, tremor, nausea, vomiting, diarrhea, grand mal seizures, heart attacks, strokes, hallucinations and DTs. Withdrawal can also include severe cravings for the drug, fatigue, lack of pleasure, anxiety, irritability, sleepiness, suicidal thoughts, and sometimes agitation or extreme suspicion or paranoia. Once acute withdrawal symptoms have subsided, post-acute withdrawal syndrome can last for months or years. Post-acute withdrawal symptoms include fatigue, depression, lack of motivation, and increased pain sensitivity. Acute and post-acute withdrawal symptoms are the primary reason drug-addicted patients return to using the drug after treatment, even when the patient has been drug-free for a significant amount of time.

[0011] Although treatments have been developed in attempts to ameliorate acute and post-acute withdrawal symptoms, such treatments do not work for all types of drugs. In addition, treatment of withdrawal may require use of other addictive substances (e.g., morphine or methadone) and that the addict attend a clinic daily for an extended amount of time. Due to the severity and duration of withdrawal symptoms, addicted patients have a high rate of relapse. There is a significant need for effective, non-addictive treatment for acute and post-acute withdrawal symptoms.
Depression

[0012] Depressive disorders include major depressive disorder and dysthymic disorder (American Psychiatric Association, 1994a; American Psychiatric Association, 1994b). Major depressive disorder is characterized by the occurrence of one or more major depressive episodes without manic or hypomanic episodes. A major depressive episode is defined as a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it can include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation. Dysthymic disorder involves a type of depression that is not severe enough to be called a major depressive episode, but that lasts much longer than major depressive disorder, without high phases.

[0013] Post-traumatic stress disorder (PTSD), as defined by DSM-III-R/IV (American Psychiatric Association, 1987; American Psychiatric Association, 1994a), requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror. Although PTSD is classified as an anxiety disorder, PTSD is unique from other anxiety disorders because of the requirement of exposure to a traumatic event.

[0014] Symptoms that occur as a result of exposure to the traumatic event include re-experiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

[0015] The CDC estimates that about 1 in 10 adults in the United States suffer from depression. High levels of depression correlate with high rates of other diseases, including
obesity, heart disease, and stroke. Similarly, PTSD affects approximately 8% of Americans at some point in their lives. More strikingly, up to 30% of people, including veterans, who spend time in war zones develop PTSD. PTSD is increasingly recognized as a major issue for U.S. troops returning from Iraq and Afghanistan, as well as those who served in previous wars, and is a potential contributor to the high rate of suicide among veterans.

[0016] Given the prevalence and impact of depression and PTSD, there is a need for treatments that address these issues. Prior to the embodiments described herein, the therapeutic dosing of ibogaine and its derivatives for treating depression and/or PTSD in humans at an acceptable QT interval prolongation has not previously been addressed, especially as it relates to dosing protocols that are effective, as well as safe.

**Tolerance To Opioid Analgesics**

[0017] Addictive opioid analgesic agents such as morphine are well-characterized and exceptionally potent analgesics. As is well known, continued use of many such opioids (especially at high doses) carries a significant risk of dependency/addiction. Indeed, potential addiction to such opioids is a serious issue that limits the therapeutic use of addictive opioids as analgesic agents. For example, the use of morphine as an analgesic is common among end stage patients suffering from serious pain where addiction is no longer a concern.

[0018] Drug tolerance to opioid analgesics is common, and may be psychological and/or physiological. A patient who has developed tolerance to the opioid analgesic is not necessarily addicted to or misusing the analgesic. Drug tolerance occurs when the patient's reaction to the drug is reduced, requiring an increase in dose to achieve the same desired effect.

[0019] Drug tolerance requires that the dosage of analgesic be increased in order to provide sustained analgesic effect. However, high doses of opioids may lead to serious complications and side effects, including physical dependence, addiction, respiratory depression, nausea, sedation, euphoria or dysphoria, decreased gastrointestinal motility, and itching.

[0020] It would be beneficial to provide a method for modulating opioid analgesic tolerance in a patient taking one or more opioid analgesics for the treatment of pain.

**Impulse Control Disorder, Anxiety-Related Disorders, Violence And/Or Anger, Or Regulating Food Intake**

[0021] Obsessive compulsive disorder (OCD) is characterized by recurrent and persistent ideas, thoughts, impulses or images (obessions) that are ego-dystonic and/or repetitive,
purposeful and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable (American Psychiatric Association, 1994a). The obsessions or compulsions cause marked distress, are time-consuming, and/or significantly interfere with social or occupational functioning.

[0022] Panic disorder is characterized by recurrent unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks (American Psychiatric Association, 1994a). A panic attack is defined as a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes. Panic disorder may or may not be associated with agoraphobia, or an irrational and often disabling fear of being out in public.

[0023] Social anxiety disorder, also known as social phobia, is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others (American Psychiatric Association, 1994a). Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

[0024] Generalized anxiety disorder is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control (American Psychiatric Association, 1994a). It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep
disturbance. The diagnostic criteria for this disorder are described in further detail in DSM-IV, which is incorporated herein by reference (American Psychiatric Association, 1994a).

[0025] Impulse control disorder is a class of psychiatric disorders involving the failure to resist a temptation, urge, or impulse (impulsivity) where such impulse is potentially harmful to the patient and/or others. The American Psychiatric Association's DSM-5 (May 2013) includes impulse control disorders "characterized by problems in emotional and behavioral self-control". These include borderline personality disorder, conduct disorder, antisocial personality disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, mood disorders, pathological gambling, pyromania, intermittent explosive disorder, kleptomania, sexual compulsion, paraphilia, internet addiction, trichotillomania, pathological skin picking, and compulsive shopping. Impulse control disorder may be related to anxiety disorder and/or OCD.

[0026] Violence and anger, particularly when out of proportion to a stimulus and/or a result of pathological anger, are associated with a number of mental disorders. These include oppositional defiant disorder, attention-deficit/hyperactivity disorder and conduct disorder (in children and adolescents), psychotic disorder, bipolar disorder, antisocial, borderline, paranoid and narcissistic personality disorders, adjustment disorder with disturbance of conduct, and intermittent explosive disorder. Pathological anger and violence account for a significant portion of violent crimes, including many high-profile crimes involving multiple victims. Highly volatile individuals are over-represented in the prison system in the United States.

[0027] Over 2/3 of adults in the U.S. are overweight, with about half of those being obese. The U.S. weight loss market is estimated to be worth over $60 billion; diet pills alone account for around $1 billion. However, many diet pills contain ingredients that are at best of dubious efficacy and at worst dangerous. Obesity greatly increases a person's risk for a variety of diseases, including coronary heart disease, high blood pressure, stroke, type 2 diabetes, abnormal levels of blood fats, metabolic syndrome, cancer, osteoarthritis, sleep apnea, reproductive issues, and gallstones.

[0028] Given the prevalence and impact of anxiety disorders, impulse control disorder, anger/violence-related disorders, and overweight/obesity, there is a need for treatments that address these issues. Prior to the embodiments described herein, the therapeutic dosing of ibogaine and its derivatives for treating anxiety disorders, impulse control disorder,
anger/violence-related disorders, or regulation of food intake in humans at an acceptable QT interval prolongation has not previously been addressed, especially as it relates to dosing protocols that are effective, as well as safe.

**SUMMARY OF THE INVENTION**

[0029] Iboiogaine has been used as a botanical preparation from the root bark of iboga tabernathe for over 100 years both as a crude preparation and as semisynthetic ibogaine, which was marketed in France until about 1970. The therapeutic use of ibogaine is limited due to potentially adverse side effects. For example, ibogaine exhibits undesirable stimulant and hallucinogenic properties, and in addition, can induce tremors. At conventional doses, ibogaine causes adverse side effects in a majority of patients receiving treatment.

[0030] 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 Iboigaine 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.

[0031] Further, prior to the embodiments described herein, the therapeutic dosing of ibogaine and its derivatives for treating opioid or opioid-like drug addiction in humans at an acceptable QT interval prolongation has not previously been addressed, especially as it relates to dosing protocols that are effective, as well as safe. A prolonged QT interval is a marker of potential ventricular tachyarrhythmia which, and can result in death. Serious complications, including ventricular tachyarrhythmia and death, can result from prolongation of the treated patient’s QT interval by ibogaine, rendering high doses of ibogaine unacceptable.

[0032] Heretofore, it was unclear whether a therapeutic dose of ibogaine could be found that resulted in QT interval prolongation within an acceptable range. It is expected that other compounds that share ibogaine’s core structure will have a similar prolongation effect on QT interval. See, U.S. Provisional Patent Application No. 61/945,746 filed February 27, 2014
entitled METHOD FOR ACUTE AND LONG-TERM TREATMENT OF DRUG ADDICTION.

Nicotine

[0033] This invention is based, in part, on the discovery that at very low doses, direct blood stream delivery of ibogaine will reduce the desire to smoke. Such dosing is well below that previously described. Direct blood stream delivery of ibogaine is contemplated to enhance the amount of ibogaine delivered to the brain, because ibogaine so administered does not initially pass through the liver before reaching the brain as it does when ingested. Direct blood stream delivery of ibogaine includes sublingual, pulmonary and intranasal delivery where the ibogaine is absorbed directly into the blood stream and then into the brain. The rapid delivery of ibogaine into the brain causes a significant reduction in the craving to smoke on a rapid basis, typically less than 15 minutes after administration. The very low doses and direct delivery from the blood stream to the brain is also contemplated to avoid significant QT prolongation or to keep the QT prolongation within the acceptable range.

[0034] Ibogaine is believed to bind to several receptors in the brain, including nicotinic acetylcholine receptors (nAChRs) and opioid receptors (e.g., μ-opioid receptors). Without being bound by theory, it is believed that the nAChR has a greater binding affinity for ibogaine than other receptors in the brain. This allows treatment of nicotine addiction and/or nicotine cravings using much lower doses of ibogaine than are currently used for the treatment of other conditions, such as opioid withdrawal. Furthermore, a nicotine addict in remission may not exhibit physical symptoms of addiction, but rather may have psychological cravings for cigarettes or other forms of nicotine, or may anticipate such cravings in certain situations. As such, and without being bound by theory, it is expected that lower amounts of ibogaine are required to treat or prevent nicotine cravings in such situations than would be required in a patient who is currently addicted to nicotine.

[0035] In one aspect, this invention relates to methods of treating nicotine addiction or preventing relapse of nicotine use, comprising administration of a therapeutic amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate of each thereof.

[0036] In one aspect, this invention relates to treating nicotine addiction in a patient in need thereof comprising administering to the patient by direct blood stream delivery a
therapeutically effective amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof. In one aspect, a therapeutically effective amount of ibogaine or derivative is from about 50 ng to less than 10 µg per kg of body weight. In some embodiments, the therapeutically effective amount of ibogaine or ibogaine derivative is administered once a day, twice a day, or more than twice a day.

[0037] In another aspect, this invention provides a method for treating nicotine addiction in a patient in need thereof comprising administering to the patient a therapeutic amount of ibogaine or an ibogaine derivative or pharmaceutically acceptable salt and/or solvate thereof, wherein the ibogaine or derivative or pharmaceutically acceptable salt and/or solvate thereof is administered by sublingual, intranasal, or intrapulmonary delivery.

[0038] In another aspect, relates to methods of preventing relapse of nicotine use, comprising administration of a prophylactic amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate of each thereof to inhibit a behavioral craving for nicotine.

[0039] In one aspect, this invention relates to preventing relapse of nicotine use in a patient in need thereof comprising administering to the patient by direct blood stream delivery a prophylactically effective amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate of each thereof. In one aspect, a prophylactically effective amount of ibogaine or derivative is from about 50 ng to less than 10 µg per kg of body weight. In some embodiments, the prophylactically effective amount of ibogaine or ibogaine derivative is administered once a day, twice a day, or more than twice a day. In some embodiments, the prophylactically effective amount is administered when the patient feels a craving, or anticipates feeling a craving, for nicotine.

[0040] In another aspect, this invention provides a method for preventing relapse of nicotine use in a patient in need thereof comprising administering to the patient a prophylactically effective amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof, wherein the ibogaine, derivative, or salt and/or solvate thereof is administered by sublingual, intranasal, or intrapulmonary delivery.

[0041] In one aspect, provided herein is a method for treating nicotine addiction 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,
wherein said therapeutically effective amount is from about 50 ng to less than 10 µg per kg body weight per day.

[0042] In one embodiment, the therapeutically effective amount is from about 50 ng to about 1 µg per kg body weight per day. In another embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered by sublingual, intranasal, or intrapulmonary delivery. In another embodiment, the therapeutically effective amount is administered once a day. In another embodiment, the therapeutically effective amount is administered two or more times per day.

[0043] In another aspect, provided herein is a method for preventing a nicotine craving in a patient in need thereof, comprising administering to the patient a prophylactically effective amount of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof, wherein said prophylactically effective amount is from about 50 ng to less than 10 µg per kg body weight per day.

[0044] In one embodiment, the patient is no longer physically addicted to nicotine. In another embodiment, the prophylactically effective amount is from about 50 ng to about 1 µg per kg body weight per day. In another embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered by sublingual, intranasal, or intrapulmonary delivery. In another embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered on an as-needed basis as determined by the subject. In another embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered before the nicotine craving occurs. In another embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered after the nicotine craving occurs.

**Alcohol**

[0045] One aspect of the current invention is predicated, at least in part, on the surprising discovery that treatment of alcohol dependence with ibogaine and derivatives thereof can be achieved with an acceptable QT interval prolongation when such compounds are administered within a narrow dosage range. Specifically, dosing an addicted patient with greater than about 1 mg/kg body weight to about 8 mg/kg body weight, provides a therapeutic reduction in withdrawal symptoms in alcohol dependent patients. Preferably, the dose range that provide both therapeutic results and an acceptable QT interval prolongation of less than
50 milliseconds in addicted humans is between about 1.3 mg per kg body weight and no more than about 4 mg per kg body weight and, more preferably between about 1.3 mg per kg body weight and no more than about 3 mg per kg body weight, or any subrange or subvalue within the aforementioned ranges.

[0046] In one aspect of the invention, the narrow therapeutic doses of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate described above do not prolong the QT interval to unacceptable levels in human patients. It is expected that alcohol dependent patients will be administered therapeutic doses of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof in a clinical setting with cardiac monitoring. In some embodiments, the patient will be pre-screened to evaluate tolerance for prolongation of QT interval, e.g., to determine whether the patient has any pre-existing cardiac conditions or other indicators which would disqualify them from treatment with ibogaine. In one embodiment, a patient who exhibits a QT interval prolongation of less than about 20 ms after treatment with one or more therapeutic doses of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof will not require further clinical monitoring.

[0047] Some aspects of the current invention are further predicated on the discovery that even lower doses of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof, for example approximately 80% or less of the therapeutic dose, may be effective for prevention of relapse of alcohol use in an addicted patient treated to ameliorate their alcohol dependence. That is, a lower dose of ibogaine can prevent a patient who is no longer physically dependent on alcohol from relapsing to use thereof. Without being bound by theory, it is believed that a patient who is no longer physically dependent on alcohol requires less ibogaine to prevent relapse at least in part because the changes made to the brain by alcohol dependence at least partially reverse when the patient detoxifies from alcohol. This lower, maintenance dose of ibogaine results in a QT interval prolongation that does not require clinical cardiac monitoring.

[0048] In some embodiments, the therapeutic dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof administered to the patient is sufficient to provide an average serum concentration of about 50 ng/mL to about 850 ng/mL, or any subrange or subvalue there between. In a preferred embodiment, the dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof administered
to the patient provides an average serum concentration of about 50 ng/mL to about 400 ng/mL.

[0049] In some embodiments, the patient is administered a high (therapeutic) dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof for a period of time to ameliorate the most significant withdraw symptoms, and then is administered a lower (maintenance) dose to prevent relapse to alcohol use. In some embodiments, the patient is administered a therapeutic dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof for a period of time to ameliorate the most significant withdraw symptoms, and then is administered a decreasing (tapered) amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof over time until the maintenance dose is reached. In some embodiments, a high initial therapeutic dose is administered, followed by administration of a lower therapeutic dose. In some embodiments, the dose of ibogaine is tapered over time from the high therapeutic dose to a lower therapeutic dose.

[0050] In some embodiments, the dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL is administered as a single dose. In some embodiments, the dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL is administered as multiple doses. In some embodiments, the aggregate dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from greater than about 1 mg/kg to about 8 mg/kg. In a preferred embodiment, the aggregate dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from greater than about 1 mg/kg to about 4 mg/kg. In another preferred embodiment, the aggregate dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from greater than about 1 mg/kg to 3 mg/kg.

[0051] In some embodiments, the serum concentration of ibogaine is sufficient to inhibit or ameliorate said dependence while maintaining a QT interval of less than 500 milliseconds (ms) during said treatment. In some embodiments, the therapeutic dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof provides prolongation of the QT interval of less than 80 ms. In one embodiment, the maintenance dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof provides prolongation of the QT interval of less than 50 ms. In some embodiments, the maintenance
dose or therapeutic dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof provides prolongation of the QT interval of less than 30 ms. In a preferred embodiment, the maintenance dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof provides prolongation of the QT interval of less than 20 ms. In a preferred embodiment, the patient is tested to determine QT interval before treatment with ibogaine, and if clinician determines that the QT prolongation would be unacceptable risk, ibogaine therapy will be contraindicated.

[0052] In one aspect, provided herein is a method for treating alcohol dependence in a human patient suffering therefrom, comprising administering to the patient a dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to ameliorate said dependence while maintaining a QT interval of less than about 500 ms during said treatment.

[0053] In one embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered as a single dose or multiple doses.

[0054] In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 1.3 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 1.5 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 2 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 2 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is about 2 mg/kg per day. In another embodiment, the dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof provides an average serum concentration of about 50 ng/mL to about 200 ng/mL.

[0055] In another embodiment, the QT interval is less than about 470 ms. In another embodiment, the QT interval is less than about 450 ms.
[0056] In another embodiment, the method further comprising selecting an addicted patient who is prescreened to evaluate tolerance for prolongation of QT interval. In another embodiment, the prescreening step comprises ascertaining that ibogaine treatment will not result in a QT interval greater than about 500 ms. In another embodiment, the prescreening step comprises ascertaining that ibogaine treatment will not result in a QT interval greater than about 470 ms. In another embodiment, the prescreening step comprises ascertaining that ibogaine treatment will not result in a QT interval greater than about 450 ms.

[0057] In another aspect, provided herein is a method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to alcohol dependence, comprising administering to the patient a dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

[0058] In one embodiment, the withdrawal symptoms are due to acute withdrawal. In another embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered as a single dose or multiple doses. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 1.3 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 1.5 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 2 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 2 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is about 2 mg/kg per day. In another embodiment, the QT interval is less than about 470 ms. In another embodiment, the QT interval is less than about 450 ms.

[0059] In another aspect, provided herein is a method to prevent relapse of alcohol abuse in a patient treated to ameliorate said abuse, said method comprising periodically administering to said patient a maintenance dosage of ibogaine, ibogaine derivative, or pharmaceutically
acceptable salt and/or solvate thereof, wherein the patient is no longer physically dependent on alcohol.

[0060] In one embodiment, the maintenance dosage is less than about 70% of a therapeutic dose, and further wherein the prolongation of the QT interval is no greater than about 30 ms. In another embodiment, the dosage is less than about 70% of the therapeutic dose, and further wherein the prolongation of the QT interval is no greater than about 20 ms.

Drug Addiction

[0061] This invention is predicated, at least in part, on the surprising discovery that treatment of addiction with ibogaine can be achieved with an acceptable QT interval prolongation when such compounds are administered within a narrow dosage range. Specifically, dosing an addicted patient with from greater than about 1 mg/kg body weight to about 4 mg/kg body weight, ibogaine will provide a therapeutic reduction in withdrawal symptoms and/or an increase in time to resumption of substance use in addicted patients without unacceptable prolongation of the patient's QT interval.

[0062] In some aspects of the invention, the dose range of ibogaine that provides both therapeutic results and an acceptable QT interval prolongation of less than 50 milliseconds in substance-addicted humans is between about 1.3 mg per kg body weight and no more than about 4 mg per kg body weight and, more preferably between about 1.3 mg per kg body weight and no more than about 3 mg per kg body weight, or any subrange or subvalue within the aforementioned ranges.

[0063] In some embodiments, the narrow therapeutic doses of ibogaine unexpectedly do not prolong the QT interval to unacceptable levels in human addicted patients. It is expected that drug addicted patients will be administered therapeutic doses of ibogaine in a clinical setting with cardiac monitoring. In some embodiments, the patient will be pre-screened to evaluate tolerance for prolongation of QT interval, e.g., to determine whether the patient has any pre-existing cardiac conditions which would disqualify them from treatment with ibogaine.

[0064] Some aspects of the current invention are further predicated on the discovery that even lower doses of ibogaine, for example approximately 80% or less of the therapeutic dose, may be effective for prevention of relapse of drug use in an addicted patient treated to ameliorate their drug use. That is, a lower dose of the compound can prevent a patient who is no longer physically addicted to a substance from relapsing to use of that substance. Without
being bound by theory, it is believed that a patient who is no longer physically addicted to the drug requires less compound to prevent relapse because the drug does not compete with the compound for receptor binding, and/or because desensitization of one or more receptors in the brain by the drug is reversed when the patient ceases to take the drug. This lower, maintenance dose results in a QT interval prolongation that does not require clinical cardiac monitoring.

[0065] In some embodiments, the therapeutic dose of ibogaine administered to the patient is sufficient to provide an average serum concentration of the compound of about 50 ng/mL to about 850 ng/mL, or any subrange or subvalue there between. In a preferred embodiment, the dose of ibogaine thereof administered to the patient provides an average serum concentration of about 50 ng/mL to about 400 ng/mL.

[0066] In some embodiments, the patient is administered a high (therapeutic) dose of ibogaine for a period of time to ameliorate the most significant withdraw symptoms, and then is administered a lower (maintenance) dose to prevent relapse to drug use. In some embodiments, the patient is administered a therapeutic dose of ibogaine for a period of time to ameliorate the most significant withdraw symptoms, and then is administered a decreasing (tapered) amount of ibogaine over time until the maintenance dose is reached. In some embodiments, a high initial therapeutic dose is administered, followed by administration of a lower therapeutic dose. In some embodiments, the dose of the compound is tapered over time from the high therapeutic dose to a lower therapeutic dose.

[0067] In some embodiments, the dose of ibogaine that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL is administered as a single dose. In some embodiments, the dose of ibogaine that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL is administered as multiple doses. In some embodiments, the aggregate dose of ibogaine is from greater than about 1 mg/kg to about 8 mg/kg. In a preferred embodiment, the aggregate dose of ibogaine is from greater than about 1 mg/kg to about 4 mg/kg. In another preferred embodiment, the aggregate dose of ibogaine is from greater than about 1 mg/kg to 3 mg/kg.

[0068] In some embodiments, the serum concentration is sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than 500 milliseconds (ms) during said treatment. In some embodiments, the therapeutic dose of ibogaine provides prolongation of the QT interval of less than 80 ms. In a preferred embodiment, the maintenance dose of
ibogaine provides prolongation of the QT interval of less than 50 ms. In some embodiments, the maintenance dose or therapeutic dose of ibogaine provides prolongation of the QT interval of less than 30 ms. In a preferred embodiment, the maintenance dose of ibogaine provides prolongation of the QT interval of less than 20 ms. In one embodiment, the QT prolongation is equivalent to or less than that observed in patients receiving methadone treatment. In a preferred embodiment, the patient is tested to determine QT interval before treatment with the compound, and if clinician determines that the QT prolongation would be unacceptable risk, therapy will be contraindicated.

**Substance Abuse**

[0069] In one aspect, provided herein is a method for treating substance abuse in a human patient addicted thereto, comprising administering to the patient a dosage of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof, preferably ibogaine, wherein the dosage provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms during said treatment.

[0070] In one embodiment, the method of claim 1 or 2, wherein the ibogaine is administered as a single dose or multiple doses. In another embodiment, the aggregate dosage of ibogaine is from about 1.3 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 1.5 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 2 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage ibogaine is from about 2 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is about 2 mg/kg per day. In another embodiment, the dosage of ibogaine provides an average serum concentration of about 50 ng/mL to about 200 ng/mL. In another embodiment, the QT interval is less than about 470 ms. In another embodiment, the QT interval is less than about 450 ms.

[0071] In one aspect, provided herein is a method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to substance addiction, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to
attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

[0072] In one embodiment, the the withdrawal symptoms are due to acute withdrawal.

[0073] In another embodiment, the ibogaine is administered as a single dose or multiple doses. In another embodiment, the aggregate dosage of ibogaine is from about 1.3 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 1.5 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 2 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 2 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is about 2 mg/kg per day. In another embodiment, the QT interval is less than about 470 ms. In another embodiment, the QT interval is less than about 450 ms.

[0074] In another aspect, provided herein is a method to prevent relapse of substance abuse in a patient treated to ameliorate said abuse, said method comprising periodically administering to said patient a maintenance dosage of ibogaine, wherein the patient is no longer abusing the substance.

[0075] In one embodiment, the dosage is less than about 70% of a therapeutic dose of ibogaine, and further wherein the prolongation of the QT interval is no greater than about 30 ms. In another embodiment, the dosage is less than about 70% of the therapeutic dose, and further wherein the prolongation of the QT interval is no greater than about 20 ms.

[0076] In one embodiment, the unit dose of ibogaine is administered in one or more dosings.

[0077] In another aspect, provided herein is a method for treating substance abuse in a patient addicted thereto, comprising selecting an addicted patient who is prescreened to evaluate tolerance for prolongation of QT interval, administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms during said treatment.
In one embodiment, the prescreening step comprises ascertaining that treatment with ibogaine will not result in a QT interval greater than about 500 ms. In another embodiment, the prescreening step comprises ascertaining that treatment with ibogaine will not result in a QT interval greater than about 470 ms. In another embodiment, the prescreening step comprises ascertaining that treatment with ibogaine will not result in a QT interval greater than about 450 ms.

In another embodiment, the addictive substance is selected from the group consisting of benzodiazepines, cannabinoids and synthetic cannabinoids, stimulants, barbiturates, gamma-hydroxybutyrate (GHB), ketamine, PCP, dextromethorphan (DXM), lysergic acid diethylamide (LSD), mescaline, anabolic steroids, and derivatives of each thereof.

Opioid Or Opioid-Like Drug Abuse

In one aspect, provided herein is a method for treating opioid or opioid-like drug abuse in a human patient addicted thereto, comprising administering to the patient a dosage of ibogaine wherein the dosage provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms during said treatment.

In another embodiment, the ibogaine is administered as a single dose or multiple doses. In another embodiment, the aggregate dosage of ibogaine is from about 1.3 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 1.5 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 2 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage ibogaine is from about 2 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is about 2 mg/kg per day. In another embodiment, the dosage of ibogaine provides an average serum concentration of about 50 ng/mL to about 200 ng/mL. In another embodiment, the QT interval is less than about 470 ms. In another embodiment, the QT interval is less than about 450 ms.

In another aspect, provided herein is a method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to opioid or opioid-like drug addiction, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to
attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

[0083] In another embodiment, the withdrawal symptoms are due to acute withdrawal. In another embodiment, the ibogaine is administered as a single dose or multiple doses. In another embodiment, the aggregate dosage of ibogaine is from about 1.3 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 1.5 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage ibogaine is from about 2 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 2 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is about 2 mg/kg per day. In another embodiment, the QT interval is less than about 470 ms. In another embodiment, the QT interval is less than about 450 ms.

[0084] In another aspect, provided herein is a method to prevent relapse of opioid or opioid-like drug abuse in a patient treated to ameliorate said abuse, said method comprising periodically administering to said patient a maintenance dosage of ibogaine wherein the patient is no longer abusing the opioid or opioid-like drug.

[0085] In one embodiment, the dosage is less than about 70% of a therapeutic dose of ibogaine and further wherein the prolongation of the QT interval is no greater than about 30 ms. In another embodiment, the dosage is less than about 70% of the therapeutic dose, and further wherein the prolongation of the QT interval is no greater than about 20 ms.

[0086] In one embodiment, the unit dose of ibogaine is administered in one or more dosings.

[0087] In one aspect, provided herein is a method for treating opioid or opioid-like drug abuse in a patient addicted thereto, comprising selecting an addicted patient who is prescreened to evaluate tolerance for prolongation of QT interval, administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms during said treatment.

[0088] In one embodiment, the prescreening step comprises ascertaining that treatment with ibogaine, ibogaine derivative, or pharmaceutically acceptable salt thereof will not result in a
QT interval greater than about 500 ms. In another embodiment, the prescreening step comprises ascertaining that treatment with ibogaine will not result in a QT interval greater than about 470 ms. In another embodiment, the prescreening step comprises ascertaining that treatment with ibogaine will not result in a QT interval greater than about 450 ms.

Pain

[0089] Pain is broadly defined as an unpleasant sensory experience associated with actual or potential tissue damage, or described in terms of such damage. The interpretation of sensory pain occurs when peripheral nerve endings called nociceptors are stimulated and subsequently transmit signals through sensory neurons in the spinal cord. The signals are then transmitted to the brain, at which point the individual becomes aware of the pain.

[0090] There are a number of pain categories and classifications, which for example, can be grouped into four categories according to the source and related nociceptors: (1) cutaneous pain; (2) somatic pain; (3) visceral pain; and (4) neuropathic pain. Other pain classifications include acute pain and chronic pain. Acute pain is defined as short-term pain or pain with an easily identifiable cause. Acute pain indicates present damage to tissue or disease and may be "fast" and "sharp" followed by aching pain. Acute pain is centralized in one area before becoming somewhat spread out. Acute pain generally responds well to medications (e.g., morphine).

[0091] Chronic pain may be medically defined as pain that has lasted six months or longer. This constant or intermittent pain has often outlived its purpose because it does not help the body to prevent injury. It is often more difficult to treat than acute pain. Expert care is generally necessary to treat any pain that has become chronic. In addition, stronger medications are typically used for extended periods in an attempt to control the pain. This can lead to drug dependency. For example, opioids are used in some instances for prolonged periods to control chronic pain. Drug tolerance, chemical dependency, and even psychological addiction may occur.

[0092] Debilitating chronic pain affects tens of millions of people annually. Accordingly, this costs hundreds of millions of dollars in terms of medication, physical therapy, and lost production. The current methods for treating chronic pain have a limited success rate and in some cases may result in chemical dependency.
Numerous treatments have been developed in attempts to ameliorate pain in its various categories. However, in many cases, treatment requires the use of addictive or habit-forming substances (e.g., morphine or methadone). Accordingly, there is a significant need for an effective, non-addictive treatment for pain, such as chronic, debilitating, nociceptive pain, that reduces the need for habit-forming pain relieving drugs.

Furthermore, human clinical studies demonstrate that the lower dosing of ibogaine has minimal impact on the alleviation of pain in patients. Thus, the previously disclosed broad range has now been found to be insufficient for at least some human therapies at the lower end of this range.

In some embodiments, the current invention is predicated on the surprising discovery that treatment with a narrow dosage range of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof, preferably of ibogaine, between greater than about 0.1 mg/kg body weight and about 8 mg/kg body weight, provides a therapeutic alleviation of pain. Preferably, the dose range that provides both therapeutic results and an acceptable QT interval prolongation of less than 50 milliseconds in humans is between about 0.1 mg per kg body weight and no more than about 3 mg per kg body weight and, more preferably between about 0.7 mg per kg body weight and no more than about 2 mg per kg body weight, or any subrange or subvalue within the aforementioned ranges.

In some embodiments, the narrow therapeutic doses of ibogaine described above do not prolong the QT interval to unacceptable levels in human patients. In some embodiments, patients are administered therapeutic doses of ibogaine in a clinical setting with cardiac monitoring. In some embodiments, the patient will be pre-screened to evaluate tolerance for prolongation of QT interval, e.g., to determine whether the patient has any pre-existing cardiac conditions which would disqualify them from treatment with ibogaine. In one embodiment, a patient who exhibits a QT interval prolongation of less than about 20 ms after treatment with one or more therapeutic doses of ibogaine will not require further clinical monitoring. In one embodiment, the patient is not monitored after administration of ibogaine.

In some embodiments, the therapeutic dose of ibogaine administered to the patient is sufficient to provide an average serum concentration of about 50 ng/mL to about 850 ng/mL, or any subrange or subvalue there between. In a preferred embodiment, the dose of ibogaine administered to the patient provides an average serum concentration of about 50 ng/mL to about 400 ng/mL.
In some embodiments, the dose of ibogaine that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL is administered as a single dose. In some embodiments, the dose of ibogaine that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL is administered as multiple doses. In some embodiments, the aggregate dose of ibogaine is from about 0.1 mg/kg to about 8 mg/kg. In one embodiment, the aggregate dose of ibogaine is from about 0.1 mg/kg to about 3 mg/kg. In another embodiment, the aggregate dose of ibogaine is from about 0.7 mg/kg to 1.5 mg/kg.

In one aspect, provided herein is a method for treating pain in a patient, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to alleviate and/or inhibit said pain while maintaining a QT interval of less than about 500 ms during said treatment.

In one embodiment, the ibogaine is administered as a single dose or multiple doses. In another embodiment, the aggregate dosage of ibogaine is from about 1.3 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 1.5 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 2 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 2 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine thereof is about 2 mg/kg per day. In another embodiment, the dosage of ibogaine provides an average serum concentration of about 50 ng/mL to about 200 ng/mL.

In one aspect, provided herein is a method for alleviating pain symptoms in a human patient susceptible to such symptoms, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to alleviate said pain symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

In one embodiment, the pain symptoms are due to chronic pain. In another embodiment, the ibogaine is administered as a single dose or multiple doses. In another embodiment, the aggregate dosage of ibogaine is from about 1.3 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 1.5 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 2 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is from about 2 mg/kg to about 3 mg/kg per day.
ibogaine is from about 2 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine is about 2 mg/kg per day.

[0103] In one embodiment, the unit dose of ibogaine is administered in one or more dosings.

**Depression**

[0104] The current invention is predicated on the surprising discovery that treatment with a narrow dosage range of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof, between greater than about 1 mg/kg body weight and about 8 mg/kg body weight, provides a therapeutic reduction in symptoms of depression and/or PTSD in affected patients. Preferably, the dose range that provide both therapeutic results and an acceptable QT interval prolongation of less than 50 milliseconds is between about 1.3 mg per kg body weight and no more than about 4 mg per kg body weight and, more preferably between about 1.3 mg per kg body weight and no more than about 3 mg per kg body weight, or any subrange or subvalue within the aforementioned ranges.

[0105] In one aspect, this invention relates to treating depression and/or PTSD in a patient in need thereof comprising administering to the patient a therapeutically effective amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof. In one embodiment, this invention treats depression. In another embodiment, this invention treats PTSD. In a preferred embodiment, the patient is not addicted to cocaine or an opiate.

[0106] In some embodiments, the therapeutic dose of ibogaine or pharmaceutically acceptable salt and/or solvate thereof administered to the patient is sufficient to provide an average serum concentration of about 50 ng/mL to about 850 ng/mL, or any subrange or subvalue there between. In a preferred embodiment, the dose of ibogaine or pharmaceutically acceptable salt and/or solvate thereof administered to the patient provides an average serum concentration of about 50 ng/mL to about 400 ng/mL. In one embodiment, the dose of ibogaine or pharmaceutically acceptable salt and/or solvate thereof administered to the patient provides an average serum concentration of about 50 ng/mL to about 200 ng/mL.

[0107] In a preferred embodiment, the narrow therapeutic doses of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate described above unexpectedly do not prolong the QT interval to unacceptable levels in human patients. In some embodiments, the patient will be pre-screened to evaluate tolerance for prolongation of QT
interval, *e.g.*, to determine whether the patient has any pre-existing cardiac conditions which would disqualify him/her from treatment with ibogaine or ibogaine derivative.

[0108] In some embodiments, the serum concentration is sufficient to inhibit or ameliorate symptoms of depression and/or PTSD while maintaining a QT interval of less than 500 milliseconds (ms) during said treatment.

[0109] In another aspect, this invention provides a method for treating depression and/or PTSD in a patient in need thereof comprising administering to the patient ibogaine, ibogaine derivative, or salt and/or solvate thereof in a sustained release manner such that the serum concentration of ibogaine or ibogaine derivative is maintained at a therapeutically effective amount for a period of about 6 hours, about 12 hours, about 18 hours, about 24 hours, about 36 hours, about 48 hours, about 72 hours, about 96 hours, or a period of time between any two of these durations.

[0110] In one aspect, provided herein is a method for treating depression and/or posttraumatic stress disorder 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, wherein the patient is not addicted to cocaine or an opiate, and further wherein the therapeutically effective amount provides an efficacious average ibogaine or ibogaine derivative serum level of between about 50 ng/mL and about 400 ng/mL while maintaining a QT interval of less than about 500 ms during said treatment.

[0111] In one embodiment, the therapeutically effective amount is between about 1 mg to about 4 mg per kg of body weight. In another embodiment, the therapeutically effective amount is between about 50 ng to less than 100 µg per kg of body weight. In another embodiment, the dosage of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof provides an average serum concentration of about 50 ng/mL to about 200 ng/mL. In another embodiment, the QT interval is less than about 470 ms. In another embodiment, the QT interval is less than about 450 ms. In another embodiment, the QT interval is less than about 420 ms. In another embodiment, the method further comprising selecting a patient who is prescreened to evaluate tolerance for prolongation of QT interval.
In another embodiment, depression is treated. In another embodiment, posttraumatic stress disorder is treated.

In another embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered by sublingual, intranasal, or intrapulmonary delivery. In another embodiment, ibogaine or ibogaine derivative or a pharmaceutically acceptable salt and/or solvate thereof is administered.

Reducing Tolerance To Opioid Analgesics

This invention is directed, in part, to the use of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof, preferably ibogaine, to modulate tolerance to addictive opioid analgesic agents in a patient who has developed or is at risk of developing a tolerance for the analgesic. In such methods, effective analgesia can be achieved in a patient while resensitizing the patient to the addictive opioid analgesic. The term "resensitizing the patient" is used herein to refer to reducing, relieving, attenuating, and/or reversing tolerance to the analgesic. In one aspect, the resensitized patient obtains therapeutic effect from a lower dose of the opioid analgesic than before resensitization. In one aspect, the resensitized patient obtains improved therapeutic effect from the same dose of the opioid analgesic compared to before resensitization.

The use of ibogaine for the modulation of tolerance to opioid analgesic agents is limited due to potentially adverse side effects. The use of ibogaine to modulate opioid tolerance is generally not favored due to the adverse side effects that can result from receiving a therapeutic dose according to conventional known methods.

In one embodiment, ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered concurrently with the opioid analgesic. In one embodiment, ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered after administration of the analgesic, for example one, two, three, four, eight, ten, twelve, 24 hours or more after administration of the analgesic. In one embodiment, one dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered. In one embodiment, two or more doses of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof are administered. In one embodiment, the opioid analgesic is interrupted for a period of time...
while ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered. In one embodiment, a non-opioid analgesic is administered while the opioid analgesic is interrupted. In one embodiment, ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof acts as an analgesic. In one embodiment, the opioid analgesic is not interrupted during ibogaine treatment.

[0117] In one aspect, provided herein is a method for modulating tolerance to an opioid analgesic in a patient undergoing opioid analgesic therapy, the method comprising interrupting or administering concurrently with said opioid analgesic therapy an amount of ibogaine, ibogaine derivative or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to re-sensitize the patient to the opioid as an analgesic while maintaining a QT interval of less than about 500 ms during said treatment.

[0118] In one embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered as a single dose or multiple doses. In another embodiment, the method further comprises interrupting the dosage of the analgesic. In another embodiment, the method further comprises administering ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof concurrently with the analgesic. In another embodiment, during concurrent administration, the dose of opioid analgesic is reduced.

[0119] In another embodiment, the dose or aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 1.3 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 1.5 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 2 mg/kg to about 4 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 2 mg/kg to about 3 mg/kg per day. In another embodiment, the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is about 2 mg/kg per day.

[0120] In another embodiment, the dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof provides an average serum
concentration of about 50 ng/mL to about 200 ng/mL. In another embodiment, the QT interval is less than about 470 ms. In another embodiment, the QT interval is less than about 450 ms.

[0121] In another embodiment, the method further comprises selecting a patient who is prescreened to evaluate tolerance for prolongation of QT interval. In another embodiment, the prescreening step comprises ascertaining that ibogaine treatment will not result in a QT interval greater than about 500 ms. In another embodiment, the prescreening step comprises ascertaining that ibogaine treatment will not result in a QT interval greater than about 470 ms. In another embodiment, the prescreening step comprises ascertaining that ibogaine treatment will not result in a QT interval greater than about 450 ms.

[0122] In another embodiment, the opioid analgesic is selected from the group consisting of fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, buprenorphine, codeine, thebaine, buprenorphine, methadone, meperidine, tramadol, tapentadol, levorphanol, sufentanil, pentazocine, oxymorphone. In another embodiment, the opioid analgesic is morphine.

**Impulse Control**

[0123] The current invention is also predicated on the surprising discovery that treatment with a narrow dosage range of ibogaine or pharmaceutically acceptable salt and/or solvate thereof, between greater than about 1 mg/kg body weight and about 4 mg/kg body weight, provides a therapeutic reduction in symptoms of anxiety disorders, impulse control disorder, anger/violence-related disorders in affected patients, or provides a therapeutic reduction in food consumption. Preferably, the dose range that provides both therapeutic results and an acceptable QT interval prolongation of less than about 50 milliseconds is between about 1.3 mg per kg body weight and no more than about 4 mg per kg body weight and, more preferably between about 1 mg per kg body weight and no more than about 3 mg per kg body weight, or any subrange or subvalue within the aforementioned ranges.

[0124] In some embodiments, the dose that provides both therapeutic results and an acceptable QT interval prolongation of less than about 50 milliseconds is between about 60 mg and about 150 mg. In some embodiments, the dose that provides both therapeutic results and an acceptable QT interval prolongation of less than about 50 milliseconds is about 100 mg. In some embodiments, the dose that provides both therapeutic results and an acceptable
QT interval prolongation of less than about 50 milliseconds is about 120 mg. In some embodiments, the dose that provides both therapeutic results and an acceptable QT interval prolongation of less than about 50 milliseconds is about 1.5 mg/kg body weight. In some embodiments, the dose that provides both therapeutic results and an acceptable QT interval prolongation of less than about 50 milliseconds is about 2 mg/kg body weight.

[0125] In some embodiments, the patient is administered an initial dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof, followed by one or more additional doses. In one embodiment, the initial dose is from about 50 mg to about 120 mg. In one embodiment, the one or more additional doses are lower than the initial dose. In one embodiment, the one or more additional doses are from about 5 mg to about 50 mg. In one embodiment, such a dosing regimen provides an average serum concentration of ibogaine of about 50 ng/mL to about 180 ng/mL. In one embodiment, the one or more additional doses maintain an average serum concentration of about 50 ng/mL to about 180 ng/mL over a period of time. In one embodiment, the one or more additional doses are administered periodically.

[0126] Furthermore, at very low doses, direct blood stream delivery of ibogaine may reduce symptoms of anxiety disorders, impulse control disorder, anger/violence-related disorders, or provide regulation of food intake. Such dosing is well below that previously described. Direct blood stream delivery of ibogaine enhances the amount of ibogaine delivered to the brain, because ibogaine does not pass through the liver as it does when ingested. Direct blood stream delivery of ibogaine includes sublingual, pulmonary and intranasal delivery where the ibogaine is absorbed directly into the blood stream and then into the brain. The rapid delivery of ibogaine into the brain, e.g. less than about 15 minutes, may cause a significant reduction in symptoms of anxiety disorders, impulse control disorder, anger/violence-related disorders, or food cravings.

[0127] In one aspect, this invention relates to treating anxiety disorders, impulse control disorder, anger/violence-related disorders, or regulation of food intake in a patient in need thereof comprising administering to the patient a therapeutically effective amount of ibogaine, ibogaine derivative, solvate, or pharmaceutically acceptable salt and/or solvate thereof. In one embodiment, this invention treats an anxiety disorder. In one embodiment, this invention treats OCD. In one embodiment, this invention treats generalized anxiety disorder. In one embodiment, this invention treats social anxiety disorder. In one
embodiment, this invention treats panic disorder. In another embodiment, this invention treats impulse control disorder. In another embodiment, this invention treats pathological anger and/or violence. In another embodiment, this invention treats anger/violence-related disorders. In another embodiment, this invention reduces pathological anger in a patient. In another embodiment, this invention reduces violent outbursts in a patient. In another embodiment, this invention regulates food intake. In one embodiment, food consumption is reduced. In one embodiment, food cravings are reduced. In a preferred embodiment, the patient is not addicted to cocaine or an opiate.

[0128] In some embodiments, the therapeutic dose of ibogaine or pharmaceutically acceptable salt and/or solvate thereof administered to the patient is sufficient to provide a serum concentration of about 100 to about 6000 ng*hour/mL. In some embodiments the therapeutic dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof administered to the patient is sufficient to provide a maximum serum concentration (Cmax) of less than about 250 ng/mL. In a preferred embodiment, the therapeutic dose provides a Cmax of about 100 ng/mL to about 200 ng/mL.

[0129] In some embodiments, the therapeutic dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof administered to the patient is sufficient to provide an average serum concentration of about 50 ng/mL to about 180 ng/mL, or any subrange or subvalue there between. In a preferred embodiment, the dose of ibogaine or pharmaceutically acceptable salt and/or solvate thereof administered to the patient provides an average serum concentration of about 50 ng/mL to about 110 ng/mL. In one embodiment, the dose of ibogaine or pharmaceutically acceptable salt and/or solvate thereof administered to the patient provides an average serum concentration of about 50 ng/mL to about 100 ng/mL. In one embodiment, the dose of ibogaine or pharmaceutically acceptable salt and/or solvate thereof administered to the patient provides an average serum concentration of less than about 50 ng/mL.

[0130] In one aspect, provided herein is a method for treating an anxiety-related disorder 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, wherein the patient is not addicted to cocaine or an opiate, and further wherein the therapeutically effective amount provides an efficacious average ibogaine serum level of
between about 50 ng/mL and about 180 ng/mL while maintaining a QT interval of less than about 500 ms during said treatment.

[0131] In one embodiment, the anxiety-related disorder is selected from the group consisting of generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, and social anxiety disorder.

[0132] In another aspect, provided herein is a method for treating an impulse control disorder 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, wherein the patient is not addicted to cocaine or an opiate, and further wherein the therapeutically effective amount provides an efficacious average ibogaine serum level of between about 50 ng/mL and about 180 ng/mL while maintaining a QT interval of less than about 500 ms during said treatment.

[0133] In one embodiment, the impulse control disorder is selected from the group consisting of borderline personality disorder, conduct disorder, antisocial personality disorder, attention deficit hyperactivity disorder, attention deficit disorder, schizophrenia, mood disorders, pathological gambling, pyromania, intermittent explosive disorder, kleptomania, sexual compulsion, paraphilia, internet addiction, trichotillomania, pathological skin picking, and compulsive shopping.

[0134] In another aspect, provided herein is a method for regulating food intake and/or attenuating food craving 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, wherein the patient is not addicted to cocaine or an opiate, and further wherein the therapeutically effective amount provides an efficacious average ibogaine serum level of between about 50 ng/mL and about 180 ng/mL while maintaining a QT interval of less than about 500 ms during said treatment.

[0135] In another aspect, provided herein is a method for treating an anger-related disorder 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, and further wherein the therapeutically effective amount provides an efficacious average ibogaine serum level of between about 50 ng/mL and about 180 ng/mL while maintaining a QT interval of less than about 500 ms during said treatment.
[0136] In one embodiment, the method comprises:
   a) administering an initial dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof, wherein the initial dose provides an average serum concentration of about 50 ng/mL to about 180 ng/mL; and
   b) administering at least one additional dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof, such that the at least one additional dose maintains the average serum concentration of about 50 ng/mL to about 180 ng/mL for a period of time.

[0137] In one embodiment, the initial dose is from about 75 mg to about 120 mg. In another embodiment, the at least one additional dose is from about 5 mg to about 25 mg. In another embodiment, the at least one additional dose is administered from about 6 hours to about 24 hours after the initial dose. In another embodiment, at least two additional doses are administered, and further wherein the additional doses are administered from about 6 hours to about 24 hours after the previous dose.

[0138] In another embodiment, the QT interval is less than about 450 ms. In another embodiment, the method further comprises selecting a patient who is prescreened to evaluate tolerance for prolongation of QT interval.

[0139] In another embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered by sublingual, buccal, intranasal, or intrapulmonary delivery.

[0140] In another embodiment, ibogaine or a pharmaceutically acceptable salt and/or solvate thereof is administered.

[0141] In some embodiments, the maintenance dose of ibogaine is 5 mg to 100 mg. In some embodiments, the maintenance dose of ibogaine is about 1.5 mg/kg body weight. In some embodiments, the maintenance dose of ibogaine is about 1 mg/kg body weight. In some embodiments, the maintenance dose of ibogaine is about 0.9 mg/kg body weight. In some embodiments, the maintenance dose of ibogaine is about 0.8 mg/kg body weight. In some embodiments, the maintenance dose of ibogaine is about 0.7 mg/kg body weight. In some embodiments, the maintenance dose of ibogaine is about 0.6 mg/kg body weight. In some embodiments, the maintenance dose of ibogaine is about 0.5 mg/kg body weight. In some embodiments, the maintenance dose of ibogaine is about 0.4 mg/kg body weight. In some
embodiments, the maintenance dose of ibogaine is about 0.3 mg/kg body weight. In some embodiments, the maintenance dose of ibogaine is about 0.2 mg/kg body weight. In some embodiments, the maintenance dose of ibogaine is about 0.1 mg/kg body weight.

Compounds Administered

[0142] In the various method, formulation and kit aspects and embodiments, in one embodiment a compound utilized herein is represented by, or ibogaine as used herein is replaced by, a compound Formula I:

![Formula I](image)

wherein

- $R$ is hydrogen or C$_i$-C$_3$-alkoxy,
- $R^1$ is hydrogen, C$_i$-C$_3$-alkyl, C$_i$-C$_3$-alkoxy, or CH$_2$-Y-CH$_3$ where Y is O or NH, and
- $X$ is H, COOH, or COOR$^2$, where R$^2$ is C$_i$-C$_6$ alkyl or (CH$_2$CH$_2$O)$_n$CH$_3$, where n = 1 to 3.

[0143] In another embodiment, ibogaine or a pharmaceutically acceptable salt and/or solvate thereof is utilized. In another embodiment, ibogaine or a pharmaceutically acceptable salt and/or solvate thereof is utilized. In another embodiment, the ibogaine, ibogaine derivative, is chosen from the group consisting of ibogaine, coronaridine, ibogamine, voacangine, 18-methoxycoronaridine, 2-methoxyethyl-18-methoxycoronaridinate, 18-methylaminocoronaridine or a pharmaceutically acceptable salt and/or solvate thereof.

[0144] In another embodiment, the compound utilized herein is chosen from the group consisting of ibogaine, coronaridine, ibogamine, voacangine, 18-methoxycoronaridine, 2-methoxyethyl-18-methoxycoronaridinate, 18-methylaminocoronaridine and a pharmaceutically acceptable salt and/or solvate.

[0145] In another embodiment, the compound utilized herein is selected from the group consisting of 16-hydroxymethyl-18-hydroxyibogaline, 16-hydroxymethyl-18-methoxyibogaline, 16-ethoxycarbonyl-18-hydroxyibogaline laurate, and 16-ethoxycarbonyl-18-hydroxyibogaline methoxyethoxymethyl ether and a pharmaceutically acceptable salt and/or solvate thereof.
In one embodiment, the ibogaine derivative is represented by Formula II:

![Formula II](image)

or a pharmaceutically acceptable salt and/or solvate thereof,

wherein

- \( R \) is hydrogen or \( C_1-C_3 \) alkoxy;
- \( R^1 \) is hydrogen, \( C_1-C_3 \) alkyl, \( C_1-C_3 \) alkoxy, \((CH_2)_mOC(0)alkyl\), \((CH_2)_mOH\), \((CH_2)_mOalkyl\), \((CH_2)_mO(CH_2)_pO(CH_2)_qO(CH_2)_rCH_3\) or \( CH_2-Y-CH_3 \) where each of \( m \), \( p \) and \( q \) is 1, 2 or 3; and \( r \) is 0, 1 or 2; \( Y \) is O or NH; and
- \( R^2 \) is H, \((CH_2)_nOH\), COOH, or COOR\(^4\), where \( R^4 \) is \( C_6 \) alkyl or \((CH_2CH_20)_nCH_3\), where \( n \) is 1, 2, or 3.

In one embodiment, the ibogaine derivative is selected from the group consisting of coronaridine, ibogamine, voacangine, 18-methoxycoronaridine, 2-Methoxyethyl-18-methoxycoronaridinate, and 18-Methylaminocoronaridine.

In one embodiment, the ibogaine derivative is selected from the group consisting of 16-hydroxymethyl-18-hydroxyibogaline, 16-hydroxymethyl-18-methoxyibogaline, 16-ethoxycarbonyl-18-hydroxyibogaline laurate, and 16-ethoxycarbonyl-18-hydroxyibogaline methoxyethoxymethyl ether.

In one embodiment, the compound is of Formula IA:

![Formula IA](image)

wherein

- \( R \) is hydrogen or \( C_1-C_3 \)-alkoxy,
- \( R^1 \) is hydrogen, \( C_1-C_3 \)-alkyl, \( C_1-C_3 \) alkoxy, or \( CH_2-Y-CH_3 \) where \( Y \) is O or NH, and
X is H, COOH, or COOR², where R² is Ci-C₆ alkyl or (CH₂CH₂O)ₙCH₃, where n = 1 to 3.

[0150] In another embodiment, the ibogaine derivative is represented by Formula II:

\[
\begin{array}{c}
\text{R} \\
\text{I}\text{I}
\end{array}
\]

II

or a pharmaceutically acceptable salt and/or solvate thereof,

wherein

\[
\begin{align*}
\text{R} & \quad \text{is OCH₃;} \\
\text{R'} & \quad \text{is CH₂CH₃;} \\
\text{and}
\end{align*}
\]

R² is COOR⁴, where R⁴ is (CH₂CH₂O)ₙCH₃, where n is 1.

[0151] When replacing ibogaine, the compounds of formula I, II, and subformulas thereof as utilized herein exclude ibogaine.

[0152] In a preferred embodiment, the compound utilized herein is:

\[
\begin{array}{c}
\text{O} \\
\text{,}
\end{array}
\]

a pharmaceutically acceptable salt thereof, or a solvate of each thereof.

**DETAILED DESCRIPTION**

[0153] It is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of this invention will be limited only by the appended claims.

[0154] The detailed description of the invention is divided into various sections only for the reader’s convenience and disclosure found in any section may be combined with that in another section. Unless defined otherwise, all technical and scientific terms used herein have
the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0155] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a plurality of compounds.

Definitions

[0156] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein the following terms have the following meanings.

[0157] The term "about" when used before a numerical designation, e.g., temperature, time, amount, concentration, and such other, including a range, indicates approximations which may vary by (+) or (-) 10%, 5% or 1% or any subrange or subvalue there between.

[0158] "Administration" refers to introducing an agent, such as ibogaine, into a patient. Typically, an effective amount is administered, which amount can be determined by the treating physician or the like. Any route of administration, such as oral, topical, subcutaneous, peritoneal, intra-arterial, inhalation, vaginal, rectal, nasal, introduction into the cerebrospinal fluid, or instillation into body compartments can be used. The agent may be administered by direct blood stream delivery, e.g. sublingual, intranasal, or intrapulmonary administration.

[0159] The related terms and phrases "administering" and "administration of," when used in connection with a compound or pharmaceutical composition (and grammatical equivalents) refer both to direct administration, which may be administration to a patient by a medical professional or by self-administration by the patient, and/or to indirect administration, which may be the act of prescribing a drug. For example, a physician who instructs a patient to self-administer a drug and/or provides a patient with a prescription for a drug is administering the drug to the patient.

[0160] "Periodic administration" or "periodically administering" refers to multiple treatments that occur on a daily, weekly, or monthly basis. Periodic administration may also refer to administration of ibogaine or salt and/or solvate thereof one, two, three, or more
times per day. Administration may be via transdermal patch, gum, lozenge, sublingual tablet, intranasal, intrapulmonary, oral administration, or other administration.

[0161] "Comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed invention. "Consisting of shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0162] As used herein, is a single bond or a double bond.

[0163] As used herein, the term "alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 12 carbon atoms, 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, and more preferably 1 to 3 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl \( \text{CH}_3 \), ethyl \( \text{CH}_2\text{CH}_3 \), n-propyl \( \text{CH}_3\text{CH}_2\text{CH}_2 \), isopropyl \( ((\text{CH}_3)_2\text{CH}) \), n-butyl \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2 \), isobutyl \( ((\text{CH}_3)_2\text{CH}) \), sec-butyl \( ((\text{CH}_3)(\text{CH}_2)\text{CH}) \), t-butyl \( ((\text{CH}_3)_3\text{C}) \), n-pentyl \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2 \), and neopentyl \( ((\text{CH}_3)_3\text{C}) \). The term "C\(_x\) alkyl" refers to an alkyl group having \( x \) carbon atoms, wherein \( x \) is an integer, for example, \( C_3 \) refers to an alkyl group having 3 carbon atoms.

[0164] "Substituted alkyl" refers to an alkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, \( \text{R}^{20}\text{C(O)}\), \( \text{NR}^{20}\text{C(O)R}^{20} \), \( \text{R}^{20}\text{C(O)O}^{\text{R}^{20}} \), \( \text{NR}^{20}\text{R}^{20} \), \( \text{O-C(O)NR}^{20}\text{R}^{20} \), \( \text{C(S)NR}^{20}\text{R}^{20} \), \( \text{S(O)NR}^{20}\text{NR}^{20}\text{R}^{20} \), \( \text{O-S(O)NR}^{20}\text{R}^{20} \), aryl, aryloxy, arylthio, azido, carboxyl, \( \text{-C(0)OR}^{21} \), \( \text{-NHC(0)OR}^{21} \), \( \text{-C(0)NOR}^{21} \), cyano, cycloalkyl, cycloalkoxy, cycloalkythio, \( \text{NR}^{20}\text{C(=NR}^{20})\text{NR}^{20}\text{R}^{20} \), halo, hydroxy, hydroxyamino, alkoxyamino, \( \text{NR}^{20}\text{NR}^{20}\text{R}^{20} \), heteroary1, heteroaryloxy, heteroarythio, heterocyclic, heterocyclyloxy, heterocyclythio, nitro, spirocycloalkyl,
S_3H, -OS(O)₂R²⁻R²⁻, -S(O)₂R²⁻, -C(S)-R⁻²⁻, thiocyanate, thiol, and alkylthio; each R²⁻ is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle, or two R²⁻ groups attached to a common atom are optionally joined together with the atom bound thereto to form a heterocycle; and each R²¹ is independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle.

[0165] "Alkoxy" refers to the group -O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, sec-butoxy, and n-pentoxy.

[0166] "Aryl" or "Ar" refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7-y1, and the like) provided that the point of attachment is at an aromatic carbon atom. Preferred aryl groups include phenyl and naphthyl.

[0167] "Substituted aryl" refers to aryl groups which are substituted with 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, -C(0)-R²⁻, -NR²⁻C(O)R²⁻, R²⁻C(O)O-, -NR²⁻R²⁻, -C(O)NR²⁻R²⁻, -C(S)NR²⁻R²⁻, -NR²⁻C(O)NR²⁻R²⁻, -NR²⁻C(S)NR²⁻R²⁻O-, -O-C(O)NR²⁻R²⁻, -S(O)₂NR²⁻R²⁻, -O-S(O)₂NR²⁻R²⁻, -NR²⁻S(O)₂NR²⁻R²⁻, -C(=NR²⁻)NR²⁻R²⁻, aryl, alkoxy, arythio, azido, carbonyl, -C(0)O-R⁻²⁻, -NR²⁻C(O)O-R⁻²⁻, -O-C(0)O-R⁻²⁻, cyano, cycloalkyl, cycloalkyloxy, cycloalkythio, -NR²⁻C(=NR²⁻)N(R²⁻)₂, halo, hydroxy, hydroxymino, alkoxyamino, -NR²⁻NR²⁻R²⁻, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclthio, nitro, spirocycloalkyl,

SO₃H, -OS(O)₂R²⁻, -S(O)₂R²⁻, -C(S)-R²⁻, thiocyanate, thiol, and alkylthio; each R²⁻ is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle, or two R²⁻ groups attached to a common atom are optionally joined together with the atom bound thereto to form a heterocycle; and each R²¹ is independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle.

[0168] "Cyano" refers to the group -CN.
"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 10 or 3 to 8 carbon atoms having single or multiple cyclic rings including fused, bridged, and spiro ring systems. One or more of the rings can be aryl, heteroaryl, or heterocyclic provided that the point of attachment is through the non-aromatic, non-heterocyclic ring carbocyclic ring. Examples of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl. Other examples of cycloalkyl groups include bicycle[2,2,2]octanyl, norbornyl, and spirobicyclo groups such as spiro[4.5]dec-8-yl.

"Substituted cycloalkyl" refers to a cycloalkyl group having from 1 to 5 or preferably 1 to 3 substituents selected from the group consisting of oxo, thione, alkyl, substituted alkyl, alkoxy, -C(0)-R, -NR2C(O)R, R2-C(O)O-, -NR2R20, -C(O)NR20R20, -C(S)NR20R20, -NR2C(O)NR20R20, -NR2C(S)NR20R20, -O-C(0)NR20R20, -S(O)2NR20R20, -O-S(O)2NR20R20, -NR20S(O)2NR20R20, -NR20C(=NR20)NR20R20, aryl, aryloxy, arylthio, azido, carboxyl, -C(0)0-R21, -NR20-C(O)0-R21, -O-C(0)0-R21, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, -NR20C(=NR20)N(R20)2, halo, hydroxy, hydroxyamino, alkoxyamino, -NR20NR20R20, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocycloxy, heterocyclithio, nitro, spirocycloalkyl, SO3H, -OS(O)2-R21, -S(O)2-R21, -C(S)-R21, thiocyanate, thiol, and alkylthio; each R20 is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle, or two R20 groups attached to a common atom are optionally joined together with the atom bound thereto to form a heterocycle; and each R21 is independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is fluoro or chloro.

"Haloalkyl" refers to alkyl groups substituted with 1 to 5, 1 to 3, or 1 to 2 halo groups, wherein alkyl and halo are as defined herein.

"Heteroaryl" refers to an aromatic group of from 5 to 14 ring atoms, including from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. In some embodiments, heteroaryl comprises 5, 6, or 7 ring atoms, including 1 to 4 heteroatoms. Such heteroaryl groups can have a single ring (e.g., pyridyl, pyridinyl or furyl) or multiple condensed rings (e.g., indoliziny or benzothienyl) wherein the
condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N→O), sulfinyl, and/or sulfonyl moieties. Preferred heteroaryls include pyridinyl, pyrrolyl, indolyl, thiophenyl, and furanyl.

[0174] "Substituted heteroaryl" refers to heteroaryl groups that are substituted with from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of the same group of substituents defined for substituted aryl.

[0175] "Heterocycle" or "heterocyclic" or "heterocycloalkyl" or "heterocyclyl" refers to a saturated or partially saturated, but not aromatic, group having from 3 to 14 ring atoms, including from 1 to 10 ring carbon atoms and from 1 to 4 ring heteroatoms selected from the group consisting of nitrogen, sulfur, or oxygen. In some embodiments, heteroaryl comprises 3, 4, 5, 6 or 7 ring atoms, including 1 to 4 heteroatoms. Heterocycle encompasses single ring or multiple condensed rings, including fused bridged and spiro ring systems. In fused ring systems, one or more the rings can be cycloalkyl, aryl, or heteroaryl provided that the point of attachment is through the non-aromatic heterocyclic ring. In one embodiment, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, sulfinyl, and/or sulfonyl moieties.

[0176] "Substituted heterocyclyl" or "substituted heterocycloalkyl" or "substituted heterocyclyl" refers to heterocyclyl groups that are substituted with from 1 to 5 or preferably 1 to 3 of the same substituents as defined for substituted cycloalkyl.

[0177] "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.
In some embodiments, the ibogaine or ibogaine derivative is represented by Formula I:

or a pharmaceutically acceptable salt and/or solvate thereof,

wherein

R is H, halo, C₁-C₃ alkyl, substituted C₁-C₃ alkyl, OR¹⁰, NH₂, NHR¹⁰, NR¹⁰R¹¹, 
NHC(0)R¹⁰, or NR¹⁰C(O)R¹¹;
R¹ is H, C₁-C₃ alkyl, substituted C₁-C₃ alkyl, C₁-C₃ alkoxy, CH₂-X-CH₃, or (CH₂)ₘR³;
R² is H, COOH, COOR⁴, (CH₂)ₙOH, CH(OH)R⁵, CH₂OR⁵, C(0)NH₂, C(0)NHR⁵,
C(0)NR⁵R⁶, C(0)NHNH₂, C(0)NHNHR⁵, C(0)NHNR⁵R⁶, C(0)NR⁵NH₂,
C(0)NR⁵NHR⁶, C(0)NR⁵NR⁶R⁷, C(0)NHNH(C(0)R°),
C(0)NHNR⁵(C(0)R°), C(0)NR⁵NH(C(0)R°), C(0)NR⁵NR⁶(C(0)R°), CN, or 
C(0)R°;
R³ is C₁-C₃ alkyl, benzyl, substituted C₁-C₃ alkyl, YH, YR₈, YC(0)R°, C(0)YR°,
C(0)NH₂, C(0)NHR°, C(0)NR°R°, NH₂, NHR°, NR°R°, NH(0)R°,
0(CH₂)ₙO(CHO₂)ₙO(CH₂)ₙCH₃ or NR°C(0)R°;
R⁴ is C₃-C₆ alkyl or (CH₂CH₂ₙ)ₙCH₃;
R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are independently alkyl or substituted alkyl;
R¹² is H, alkyl, or substituted alkyl;
R¹³ is H, OR¹⁰, alkyl, or substituted alkyl;
X is O or NH;
Y is O or S;
m is an integer selected from 0-8;
each of n, p and q is 1, 2 or 3; and
r is 0, 1 or 2.
In some embodiments, the ibogaine or ibogaine derivative is represented by Formula II:

or a pharmaceutically acceptable salt and/or solvate thereof,

wherein

R is hydrogen or C1-C3 alkoxy,

R1 is hydrogen, C1-C3 alkyl, C1-C3 alkoxy, \((\text{CH}_2)_m\text{OC}(0)\text{alkyl}, \quad \text{or}\quad \text{CH}_2\text{CH}_{2}\text{OH}\),

(CH2)m Oalkyl, \((\text{CH}_2)_m\text{O}(\text{CH}_2)p\text{O}(\text{CH}_2)\text{qO}(\text{CH}_2)_r\text{CH}_3\) or \(\text{CH}_2\text{Y-CH}_3\) where each of m, p and q is 1, 2 or 3; and r is 0, 1 or 2, Y is O or NH, and

R2 is H, \((\text{CH}_2)_n\text{OH}\), COOH, or COOR4, where R4 is C1-C6 alkyl or \((\text{CH}_2\text{CH}_2)\text{nCH}_3\),

where n is 1, 2, or 3.

In one embodiment, R is methoxy. In one embodiment, R1 is ethyl. In one embodiment, R1 is methoxy. In one embodiment, R1 is CH2-Y-CH3 where Y is O. In one embodiment, R1 is CH2-Y-CH3 where Y is NH. In one embodiment, R2 is hydrogen. In one embodiment, R2 is COOR4 and R4 is methyl. In one embodiment, n = 1.

In a preferred embodiment, R, R1 and R2 are all not hydrogen. In one embodiment, when R is methoxy and R1 is hydrogen, then R2 is COOH or COOR4. In another embodiment, when R is methoxy and R1 is hydrogen, then X is COOR4 where R4 is \((\text{CH}_2\text{CH}_2\text{OH})\text{CH}_3\).

In one embodiment, R12 is hydrogen.

In one embodiment, R1 is H. In one embodiment, R1 is C1-C3 alkyl, such as ethyl.

In one embodiment, R1 is \((\text{CH}_2\text{CH}_2)\text{OH}\). In one embodiment, R1 is \((\text{CH}_2\text{CH}_2)\text{OCH}_3\). In one embodiment, R1 is \((\text{CH}_2\text{CH}_2)\text{OCH}_2\text{Ph}\). In one embodiment, R1 is \((\text{CH}_2\text{CH}_2)\text{OC}(0)\text{alkyl}\). In one embodiment, R1 is \((\text{CH}_2\text{CH}_2)\text{o(\text{CH}_2)p\text{O}(\text{CH}_2)qO(\text{CH}_2)_r\text{CH}_3}\).

In one embodiment, R2 is \((\text{CH}_2\text{OH})\text{CH}(\text{OH})\text{R}^5\). In one embodiment, R2 is \((\text{CH}_2\text{OR})^5\). In one embodiment, R2 is \((\text{CO}_2)\text{R}^5\). In one embodiment, R2 is \((\text{C}(0)\text{NH}_2\text{)}\text{C}(0)\text{NHR^5}\text{, or C}(0)\text{NR^5R^6}\text{. In one embodiment, R2 is C}(0)\text{NHNH}_2\text{, C}(0)\text{NHNHR^5}\text{, C}(0)\text{NHR^5NH}_2\text{, C}(0)\text{NHR^5R^6}\text{, or C}(0)\text{NR^5NR^5R}^7\text{. In one embodiment, R2}

43
is C(0)NHNH(C(0)R ₅), C(0)NHNR ₅(C(0)R ₆), C(0)NR ₅NH(C(0)R ₆), or C(0)NR ₅NR ₆(C(0)R ⁷). In one embodiment, R² is C(0)R ⁵.

[0184] In some embodiments, the ibogaine or ibogaine derivative is selected from:

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>coronaridine</td>
<td><img src="image1.png" alt="Coronaridine" /></td>
</tr>
<tr>
<td>18-hydroxy coronaridine</td>
<td><img src="image2.png" alt="18-hydroxy coronaridine" /></td>
</tr>
<tr>
<td>18-methoxy coronaridine</td>
<td><img src="image3.png" alt="18-methoxy coronaridine" /></td>
</tr>
<tr>
<td>18-benzyloxy coronaridine</td>
<td><img src="image4.png" alt="18-benzyloxy coronaridine" /></td>
</tr>
<tr>
<td>18-hydroxy coronaridine laurate</td>
<td><img src="image5.png" alt="18-hydroxy coronaridine laurate" /></td>
</tr>
<tr>
<td>18-hydroxy coronaridine methoxyethoxymethyl ether</td>
<td><img src="image6.png" alt="18-hydroxy coronaridine methoxyethoxymethyl ether" /></td>
</tr>
<tr>
<td>18-hydroxy coronaridine acetate</td>
<td><img src="image7.png" alt="18-hydroxy coronaridine acetate" /></td>
</tr>
<tr>
<td>Compound</td>
<td>Structure Image</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>voacangine</td>
<td><img src="image" alt="voacangine" /></td>
</tr>
<tr>
<td>18-hydroxyvoacangine</td>
<td><img src="image" alt="18-hydroxyvoacangine" /></td>
</tr>
<tr>
<td>18-methoxyvoacangine</td>
<td><img src="image" alt="18-methoxyvoacangine" /></td>
</tr>
<tr>
<td>18-benzyloxyvoacangine</td>
<td><img src="image" alt="18-benzyloxyvoacangine" /></td>
</tr>
<tr>
<td>18-hydroxyvoacangine laurate</td>
<td><img src="image" alt="18-hydroxyvoacangine laurate" /></td>
</tr>
<tr>
<td>18-hydroxyvoacangine acetate</td>
<td><img src="image" alt="18-hydroxyvoacangine acetate" /></td>
</tr>
<tr>
<td>18-hydroxyvoacangine methoxyethoxymethyl ether</td>
<td><img src="image" alt="18-hydroxyvoacangine methoxyethoxymethyl ether" /></td>
</tr>
<tr>
<td>conopharyngine</td>
<td><img src="image" alt="conopharyngine" /></td>
</tr>
<tr>
<td>18-hydroxyconopharyngine</td>
<td><img src="image" alt="18-hydroxyconopharyngine" /></td>
</tr>
<tr>
<td>Name</td>
<td>Structure</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>18-methoxyconopharyngine</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>18-benzylxyconopharyngine</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>18-hydroxyconopharyngine laurate</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>18-hydroxyconopharyngine acetate</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>18-hydroxyconopharyngine methoxyethoxymethyl ether</td>
<td><img src="image5" alt="Structure" /></td>
</tr>
<tr>
<td>ibogamine</td>
<td><img src="image6" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogamine</td>
<td><img src="image7" alt="Structure" /></td>
</tr>
<tr>
<td>16-hydroxymethyl-18-hydroxyibogamine</td>
<td><img src="image8" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-methoxyibogamine</td>
<td><img src="image9" alt="Structure" /></td>
</tr>
<tr>
<td>Compound</td>
<td>Structure</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>16-hydroxymethyl-18-methoxyibogamine</td>
<td><img src="image1.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-benzyloxyibogamine</td>
<td><img src="image2.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogamine laurate</td>
<td><img src="image3.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogamine acetate</td>
<td><img src="image4.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogamine methoxyethoxymethyl ether</td>
<td><img src="image5.png" alt="Structure" /></td>
</tr>
<tr>
<td>ibogaine</td>
<td><img src="image6.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogaine</td>
<td><img src="image7.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-hydroxymethyl-18-hydroxyibogaine</td>
<td><img src="image8.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-methoxyibogaine</td>
<td><img src="image9.png" alt="Structure" /></td>
</tr>
<tr>
<td>Compound</td>
<td>Structure</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>16-hydroxymethyl-18-methoxyibogaine</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-benzyloxyibogaine</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogaine laurate</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogaine acetate</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogaine methoxyethoxymethyl ether</td>
<td><img src="image5" alt="Structure" /></td>
</tr>
<tr>
<td>ibogaline</td>
<td><img src="image6" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogaline</td>
<td><img src="image7" alt="Structure" /></td>
</tr>
<tr>
<td>16-hydroxymethyl-18-hydroxyibogaline</td>
<td><img src="image8" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-methoxyibogaline</td>
<td><img src="image9" alt="Structure" /></td>
</tr>
<tr>
<td>Compounds</td>
<td>Structures</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>16-hydroxymethyl-18-methoxyibogaline</td>
<td><img src="image1.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-benzyloxyibogaline</td>
<td><img src="image2.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogaline laurate</td>
<td><img src="image3.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogaline acetate</td>
<td><img src="image4.png" alt="Structure" /></td>
</tr>
<tr>
<td>16-ethoxycarbonyl-18-hydroxyibogaline methoxyethoxymethyl ether</td>
<td><img src="image5.png" alt="Structure" /></td>
</tr>
</tbody>
</table>

and pharmaceutically acceptable salts and/or solvates thereof.

[0185] This invention is not limited to any particular chemical form of the compounds, and the drug may be given to patients either as a free base, solvate, or as a pharmaceutically acceptable acid addition salt. In the latter case, the hydrochloride salt is generally preferred, but other salts derived from organic or inorganic acids may also be used. Examples of such acids include, without limitation, those described below as "pharmaceutically acceptable salts" and the like.

[0186] In one embodiment, the ibogaine derivative is:

![Structure](image6.png)

(coronaridine),
(ibogamine),
(voacangine),
(18-methoxycoronaridine, 18-MC),
(2-Methoxyethyl-18-methoxycoronaridinate, ME-18-MC), or
(18-Methylaminocoronaridine, 18-MAC).

[0187] "Pharmaceutically acceptable composition" refers to a composition that is suitable for administration to a mammal, particularly, a human. Such compositions include various excipients, diluents, carriers, and such other inactive agents well known to the skilled artisan.

[0188] "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts, including pharmaceutically acceptable partial salts, of a compound, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methane sulfonic acid, phosphorous acid, nitric acid, perchloric acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, aconitic acid, salicylic acid, thalic acid, embonic acid, enanthic acid, oxalic acid and the like, and when the molecule
contains an acidic functionality, include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like.

[0189] A "pharmaceutically acceptable solvate" or "hydrate" of a compound of the invention means a solvate or hydrate complex that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound, and includes, but is not limited to, complexes of a compound of the invention with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

[0190] As used herein the term "solvate" is taken to mean that a solid-form of a compound that crystallizes with one or more molecules of solvent trapped inside. A few examples of solvents that can be used to create solvates, such as pharmaceutically acceptable solvates, include, but are certainly not limited to, water, methanol, ethanol, isopropanol, butanol, Cl-C6 alcohols in general (and optionally substituted), tetrahydrofuran, acetone, ethylene glycol, propylene glycol, acetic acid, formic acid, water, and solvent mixtures thereof. Other such biocompatible solvents which may aid in making a pharmaceutically acceptable solvate are well known in the art and applicable to the present invention. Additionally, various organic and inorganic acids and bases can be added or even used alone as the solvent to create a desired solvate. Such acids and bases are known in the art. When the solvent is water, the solvate can be referred to as a hydrate. Further, by being left in the atmosphere or recrystallized, the compounds of the present invention may absorb moisture, may include one or more molecules of water in the formed crystal, and thus become a hydrate. Even when such hydrates are formed, they are included in the term "solvate". Solvate also is meant to include such compositions where another compound or complex co-crystallizes with the compound of interest.

[0191] "Therapeutically effective amount" or "therapeutic amount" refers to an amount of a drug or an agent that, when administered to a patient suffering from a condition, will have the intended therapeutic effect, e.g., alleviation, amelioration, palliation or elimination of one or more manifestations of the condition in the patient. The therapeutically effective amount will vary depending upon the patient and the condition being treated, the weight and age of the subject, the severity of the condition, the salt, solvate, or derivative of the active drug portion chosen, the particular composition or excipient chosen, the dosing regimen to be followed, timing of administration, the manner of administration and the like, all of which can be
determined readily by one of ordinary skill in the art. The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. For example, and without limitation, a therapeutically effective amount of ibogaine, in the context of treating nicotine dependency, refers to an amount of the ibogaine that attenuates the dependency and/or statistically presents little or no risk of relapse to nicotine use. For example, and without limitation, a therapeutically effective amount of ibogaine, in the context of treating alcohol dependency, refers to an amount of ibogaine that attenuates the dependency and/or symptoms of acute withdrawal for at least 2 hours beyond control (placebo), at least 5 hours beyond control, and preferably at least 10 hours beyond control. For example, and without limitation, a therapeutically effective amount of ibogaine in the context of treating opioid or opioid-like drug dependency, refers to an amount of compound that attenuates the dependency and/or symptoms of acute withdrawal for at least 2 hours beyond control (placebo), at least 5 hours beyond control, and preferably at least 10 hours beyond control. For example, and without limitation, a therapeutically effective amount of ibogaine in the context of treating drug dependency, refers to an amount of compound that attenuates the dependency and/or symptoms of acute withdrawal for at least 2 hours beyond control (placebo), at least 5 hours beyond control, and preferably at least 10 hours beyond control. For example, and without limitation, a therapeutically effective amount of ibogaine, in the context of treating pain, refers to an amount of ibogaine that provides immediate and/or sustained pain relief for at least 2 hours beyond control (placebo), at least 5 hours beyond control, and preferably at least 10 hours beyond control. For example, and without limitation, a therapeutically effective amount of an agent, in the context of treating anxiety disorders, impulse control disorder, and/or anger/violence-related disorders, refers to an amount of the agent that attenuates the anxiety disorder, impulse control disorder, or anger/violence-related disorders, and/or symptoms thereof, in the patient. A therapeutically effective amount of an agent, in the context of regulating food intake and/or controlling food cravings, refers to an amount of the agent that reduces the patient’s food intake and/or reduces food cravings in the patient.

A "therapeutic level" of a drug is an amount of ibogaine that is sufficient to treat a disease or disorder or symptoms of a disease or disorder or to treat, prevent, or attenuate a disease or disorder or symptoms of a disease or disorder, but not high enough to pose any significant risk to the patient. Therapeutic levels of drugs can be determined by tests that
measure the actual concentration of the compound in the blood of the patient. This concentration is referred to as the "serum concentration." Where the serum concentration of ibogaine is mentioned, it is to be understood that the term "ibogaine" encompasses any form of ibogaine, including derivatives thereof.

[0193] As defined herein, a "prophylactically effective amount" of a drug is an amount, typically less than the therapeutically effective amount, that provides attenuation and/or prevention of a disease or disorder or symptoms of a disease or disorder in a patient. For example, the prophylactically effective amount of the compound is expected to be less than the therapeutically effective amount because the level of inhibition does not need to be as high in a patient who is no longer physically addicted to nicotine. For example, a prophylactically effective amount is preferably 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% less than a therapeutically effective amount. However, a prophylactically effective amount may be the same as the therapeutically effective amount, for example when a patient who is physically addicted to nicotine is administered ibogaine to attenuate cravings for a period of time when nicotine use is not feasible. The prophylactically effective amount may vary for different a diseases or disorders or symptoms of different diseases or disorders.

[0194] As defined herein, a "maintenance amount" of a drug is an amount, typically less than the therapeutically effective amount that provides attenuation and/or prevention of a disease or disorder or symptoms of a disease or disorder in a patient. The maintenance amount of the compound is expected to be less than the therapeutically effective amount because the level of inhibition does not need to be as high in a patient who is no longer manifests a disease or disorder or symptoms of a disease or disorder. For example, a maintenance amount is preferably 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% less than a therapeutically effective amount. However, a prophylactically effective amount may be the same as the therapeutically effective amount, for example when a patient who is physically addicted to nicotine is administered ibogaine to attenuate cravings for a period of time when nicotine use is not feasible., or any subvalue or subrange there between.

[0195] "Treatment", "treating", and "treat" are defined as acting upon a disease, disorder, or condition with ibogaine to reduce or ameliorate harmful or any other undesired effects of the disease, disorder, or condition and/or its symptoms. "Treatment," as used herein, covers the treatment of a human patient, and includes: (a) reducing the risk of occurrence of the condition in a patient determined to be predisposed to the condition but not yet diagnosed as
having the condition, (b) impeding the development of the condition, and/or (c) relieving the condition, i.e., causing regression of the condition and/or relieving one or more symptoms of the condition. "Treating" or "treatment of a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results such as the reduction of symptoms. For purposes of this invention, beneficial or desired clinical results include, but are not limited to: treating nicotine addiction; treating, preventing, and/or attenuating cravings for nicotine; and preventing relapse of nicotine use. This includes reducing or eliminating smoking in the patient, and/or reducing or eliminating symptoms of withdrawal, cravings, and the like. For some purposes of this invention, beneficial or desired clinical results include, but are not limited to: treating substance addiction; treating, preventing, and/or attenuating acute withdrawal symptoms; treating, preventing, and/or attenuating long-term (post-acute) withdrawal symptoms; and preventing relapse of substance use. For purposes of certain aspects of this invention, beneficial or desired clinical results include, but are not limited to: pain relief in all categories and classifications of pain; treating, alleviating and/or preventing acute and/or chronic pain; treating, alleviating and/or preventing cutaneous, somatic, visceral and/or neuropathic pain; and preventing the recurrence of long-term pain.

[0196] "Periodic administration" or "periodically administering" refers to multiple treatments that occur on a daily, weekly, or monthly basis. Periodic administration may also refer to administration of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof one, two, three, or more times per day. Administration may be via transdermal patch, gum, lozenge, sublingual tablet, intranasal, intrapulmonary, oral administration, or other administration.

[0197] As used herein, the terms "addiction", "abuse", and "dependence" are used interchangeably to refer to the patient's inability to stop using nicotine, alcohol, a drug, or the like, even when it would be in his/her best interest to stop. A patient may be physically and/or behaviorally addicted to a substance. The DSMIV-TR criteria for dependency include:

Dependence or significant impairment or distress, as manifested by 3 or more of the following during a 12 month period:

1. Tolerance or markedly increased amounts of the substance to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount of substance
2. Withdrawal symptoms or the use of certain substances to avoid withdrawal symptoms

3. Use of a substance in larger amounts or over a longer period than was intended

4. Persistent desire or unsuccessful efforts to cut down or control substance use

5. Involvement in chronic behavior to obtain the substance, use the substance, or recover from its effects

6. Reduction or abandonment of social, occupational or recreational activities because of substance use

7. Use of substances even though there is a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

[0198] As used herein, the term "nicotine addict in remission" refers to any patient who has quit using nicotine for a period of time. As used herein, a nicotine addict in remission includes any person who was previously addicted to nicotine in any form, including but not limited to cigarettes, electronic cigarettes or vaporizers ("vaping"), chewing tobacco, cigars, snuff, pipes, hookahs, and the like. The period of time since the nicotine addict in remission quit using nicotine may be short, for example one day to a few weeks, or longer-term, for example months or years. Preferably, the patient has quit using nicotine long enough to no longer exhibit physical symptoms of nicotine addiction. The patient may exhibit psychological symptoms of nicotine addiction. In some embodiments, the patient does not exhibit psychological symptoms of nicotine addiction.

[0199] As used herein, the term "patient" refers to mammals and includes humans and non-human mammals.

[0200] As used herein, the terms "addictive substance", "drug", "addictive drug" and the like refer to drugs and other substances whose use results in addiction in at least a subset of individuals who use them. Addictive substances include, without limitation, benzodiazepines (including chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, prazepam, lorazepam, lormetazepam, oxazepam, temazepam, clonazepam, flunitrazepam, nimetazepam, nitrazepam, adinazolam, alprazolam, estazolam, triazolam, climazolam, loprazolam, and
midazolam), cannabinoids and synthetic cannabinoids, stimulants (including amphetamine, methylphenidate, dexamphetamine, dextroamphetamine, mixed amphetamine salts, dextromethamphetamine, lisdexamfetamine, modafnil, adrafinil, armodafinil, caffeine, ephedrine, methylenedioxymethamphetamine, methylenedioxypyrovalerone, mephedrone, phenylpropanolamine, propylhexadrine, pseudoephedrine, and khat), barbiturates (including allobarbital, amobarbital, aprobarbital, alphenal, barbital, brallobarbital, pentobarbital, phenobarbital, and secobarbital), gamma-hydroxybutyrate (GHB), ketamine, opiate, opioid, opioid-like drug, PCP, dextromethorphan (DXM), lysergic acid diethylamide (LSD), mescaline, anabolic steroids, and derivatives of each thereof. Addictive substances may be illicit drugs, prescription drugs prone to abuse, or other legal drugs prone to abuse."

[0201] As used herein, the term "opiate" refers to naturally-occurring alkaloids found in the opium poppy. These include codeine, morphine, oripavine, pseudomorphine, and thebaine. Also included are opium, opium poppy, poppy straw, and extracts and concentrates thereof.

[0202] As used herein, the term "opioid" refers to naturally-occurring opiates and synthetic or semi-synthetic opioids that have psychoactive effects. Non-limiting examples include acetyl-alpha-methylphentanyl, acetylmethadol, alfentanil, allylprodine, alphacetylmethadol, alphamethadol, alpha-methylfentanyl, alpha-methylthiofentanyl, alphaprodine, anileridine, benzylmorphine, benzethidine, betacetylmethadol, beta-hydroxyfentanyl, beta-hydroxy-3-methylfentanyl, betameprodine, betacetylmethadol, beta-hydroxyfentanyl, beta-hydroxy-3-methylfentanyl, betameprodine, betamethadol, betaprodine, bezitramide, buprenorphine, butorphanol, carfentanil, clonitazene, codeine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diam bromide, diamorphine, diethylthiambutene, dihydrocodeine, dihydroetorphine, dihydromorphine, dimenoxadol, dimephetanol, dimethyl thiambutene, dioxaphetyl butyrate, diphenoxylate, difenoxin, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, etoxeridine, fentanyl, furethidine, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, lev-o-alphacetylmethadol, levomethorphan, levorphanol, levophenacylmorphan, levomoramide, lofentanil, loperamide, laudanum, meperidine, meptazinol, metazocine, methadone, 3-methylfentanyl, 3-methylthiofentanyl, metopon, morphine, morpheridine, MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), myrophine, narceine, nicomorphine, noracymethadol, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum,
para-fluorofentanyl, paregoric, PEPAP (1-(-2-phenethyl)-4-phenyl-4-acetoxypiperidine),
pentazocine, phenadoxone, phenampromide, phenomorphan, phenazocine, phenoperidine,
piminodine, pirirtramide, propeptazine, promedol, properidine, propiram, propoxypheine,
racemoramide, racemethorphan, racemorphan, remifentanil, sufentanil, tapentadol, thebaine,
thiofentanyl, tilidine, tramadol, trimeperidine, mixtures of any of the foregoing, salts of any
of the foregoing, derivatives of any of the foregoing, and the like. The term opioids also
encompasses opioid intermediates, including 4-cyano-2-dimethylamino-4,4-diphenyl butane,
2-methyl-3-morpholino-1,1-diphenylpropane-carboxylic acid, 4-cyano-1-methyl-4-
phenylpiperidine, ethyl-4-phenylpiperidine-4-carboxylate, and 1-methyl-4-phenylpiperidine-
4-carboxylic acid. Many opioids are Schedule I or Schedule II drugs in the US.

[0203] As used herein, the term "opioid-like drug" refers to any illicit drug that binds to one
or more opioid receptor and causes opioid-like addiction. Acute and long-term withdrawal
symptoms from cessation of use of such drugs may be similar to those from cessation of
opioids. Opioid-like drugs include amphetamine, methamphetamine, ketamine, and cocaine.

[0204] Obsessive compulsive disorder (OCD) is characterized by recurrent and persistent
ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive,
purposeful and intentional behaviors (compulsions) that are recognized by the person as
excessive or unreasonable (American Psychiatric Association, 1994a). The obsessions or
compulsions cause marked distress, are time-consuming, and/or significantly interfere with
social or occupational functioning.

[0205] Panic disorder is characterized by recurrent unexpected panic attacks and associated
concern about having additional attacks, worry about the implications or consequences of the
attacks, and/or a significant change in behavior related to the attacks (American Psychiatric
Association, 1994a). A panic attack is defined as a discrete period of intense fear or
discomfort in which four (or more) of the following symptoms develop abruptly and reach a
peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2)
sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5)
feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling
dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or
depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of
dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes. Panic
disorder may or may not be associated with agoraphobia, or an irrational and often disabling fear of being out in public.

[0206] Social anxiety disorder, also known as social phobia, is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others (American Psychiatric Association, 1994a). Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

[0207] Generalized anxiety disorder is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control (American Psychiatric Association, 1994a). It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance. The diagnostic criteria for this disorder are described in further detail in DSM-IV, which is incorporated herein by reference (American Psychiatric Association, 1994a).

[0208] Impulse control disorder is a class of psychiatric disorders involving the failure to resist a temptation, urge, or impulse (impulsivity) where such impulse is potentially harmful to the patient and/or others. The American Psychiatric Association's DSM-5 (May 2013) includes impulse control disorders "characterized by problems in emotional and behavioral self-control". These include borderline personality disorder, conduct disorder, antisocial personality disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, mood disorders, pathological gambling, pyromania, intermittent explosive disorder, kleptomania, sexual compulsion, paraphilia, internet addiction, trichotillomania, pathological skin picking, and compulsive shopping. Impulse control disorder may be related to anxiety disorder and/or OCD.

[0209] Violence and anger, particularly when out of proportion to a stimulus and/or a result of pathological anger, are associated with a number of mental disorders. These include oppositional defiant disorder, attention-deficit/hyperactivity disorder and conduct disorder (in
children and adolescents), psychotic disorder, bipolar disorder, antisocial, borderline, paranoid and narcissistic personality disorders, adjustment disorder with disturbance of conduct, and intermittent explosive disorder. Pathological anger and violence account for a significant portion of violent crimes, including many high-profile crimes involving multiple victims. Highly volatile individuals are over-represented in the prison system in the United States.

[0210] As used herein, the term "pain" refers to all categories and classifications of pain, which are summarized below for purposes of illustration. First, cutaneous pain is caused by injury to the skin or superficial tissues. Cutaneous nociceptors terminate just below the skin, and due to the high concentration of nerve endings, produce a well-defined, localized pain of short duration. Example injuries that produce cutaneous pain include paper cuts, minor burns (e.g., first degree burns) and superficial lacerations.

[0211] Second, somatic pain originates from ligaments, tendons, bones, blood vessels, and even nerves themselves, and is detected with somatic nociceptors. The scarcity of nociceptors in these areas produces a sharp, aching, pain of longer duration than cutaneous pain and somewhat less localized. Examples include a sprained ankle or broken bones.

[0212] Third, visceral pain originates from body organs. Visceral nociceptors are located within body organs and internal cavities. Similar to somatic pain, a scarcity of nociceptors in these areas produces a pain usually more aching and of a longer duration than somatic pain. Visceral pain may be more difficult to localize. Injuries to visceral tissue may exhibit "referred" pain, where the sensation is localized to an area completely unrelated to the site of injury. Myocardial ischaemia (i.e., the loss of blood flow to a part of the heart muscle tissue) is an example of referred pain; the sensation can occur in the upper chest as a restricted feeling, or as an ache in the left shoulder, arm, or hand. Another example of referred pain is phantom limb pain. Phantom limb pain is the sensation of pain from a limb that a person no longer has or from which the person no longer receives physical signals. This phenomena—also known as deafferentation pain—is almost universally reported by amputees and quadriplegics.

[0213] Fourth, neuropathic pain (e.g., "neuralgia") can occur as a result of injury or disease to the nerve tissue itself. The injury or disease can disrupt the ability of the sensory nerves to transmit correct information to the thalamus or cortex. Consequently, the brain interprets painful stimuli even though there is no obvious or documented physiologic cause for the pain.
[0214] Other pain classifications include acute pain and chronic pain. Acute pain is defined as short-term pain or pain with an easily identifiable cause. Acute pain indicates present damage to tissue or disease and may be "fast" and "sharp" followed by aching pain. Acute pain is centralized in one area before becoming somewhat spread out. Acute pain generally responds well to medications (e.g., morphine).

[0215] Chronic pain may be medically defined as pain that has lasted six months or longer. This constant or intermittent pain has often outlived its purpose because it does not help the body to prevent injury. It is often more difficult to treat than acute pain. Expert care is generally necessary to treat any pain that has become chronic. In addition, stronger medications are typically used for extended periods in an attempt to control the pain. This can lead to drug dependency. For example, opioids are used in some instances for prolonged periods to control chronic pain. Drug tolerance, chemical dependency, and even psychological addiction may occur.

[0216] The therapeutically effective amount of the compound may be higher or lower, depending on the route of administration used. For example, when direct blood administration (e.g., sublingual, pulmonary and intranasal delivery) is used, a lower dose of the compound is administered. In one aspect, a therapeutically effective amount of ibogaine or derivative is from about 50 ng to less than 100 µg per kg of body weight. Where other routes of administration are used, a higher dose of the compound is administered. In one embodiment, the therapeutically effective amount of the compound is from greater than about 1 mg to about 8 mg per kg of body weight per day.

[0217] As used herein, the term "QT interval" refers to the measure of the time between the start of the Q wave and the end of the T wave in the electrical cycle of the heart. Prolongation of the QT interval refers to an increase in the QT interval.

[0218] "Nociceptive pain" refers to pain that is sensed by nociceptors, which are the nerves that sense and respond to parts of the body suffering from a damage. The nociceptors can signal tissue irritation, impending injury, or actual injury. When activated, they transmit pain signals (via the peripheral nerves as well as the spinal cord) to the brain. Nociceptive pain is typically well localized, constant, and often has an aching or throbbing quality. A subtype of nociceptive pain includes visceral pain and involves the internal organs. Visceral pain tends to be episodic and poorly localized. Nociceptive pain may be time limited; when the tissue damage heals, the pain typically resolves. However, nociceptive pain related to arthritis or
cancer may not be time limited. Nociceptive pain tends to respond to treatment with opiate analgesics, such as, for example, buprenorphin, codeine, hydrocodone, oxycodone, morphine, and the like. Examples of nociceptive pain include, without limitation, pains from sprains, bone fractures, burns, bumps, bruises, inflammatory pain from an infection or arthritic disorder, pains from obstructions, cancer pain, and myofascial pain related to abnormal muscle stresses.

[0219] "Neuropathic pain" refers to chronic pain, often due to tissue injury. Neuropathic pain is generally caused by injury or damage to nerve fibers. It may include burning or coldness, "pins and needles" sensations, numbness and/or itching. It may be continuous and/or episodic. Neuropathic pain is difficult to treat, but opioids, including, without limitation, methadone, tramadol, tapentadol, oxycodone, methadone, morphine, levorphanol, and the like. Causes of neuropathic pain include, without limitation, alcoholism; amputation; back, leg, and hip problems; chemotherapy; diabetes; facial nerve problems; HIV/AIDS; multiple sclerosis; shingles; spine surgery; trigeminal neuralgia; fibromyalgia; and the like. In some cases, the cause of neuropathic pain may be unclear or unknown.

[0220] "Addictive" refers to a compound that, when administered to a mammal over a period of time, creates dependency in the mammal to that compound. The dependence can be physiological and/or psychological. A therapeutic effect of an addictive compound on a mammal may decrease with prolonged administration of the addictive compound, which is a non-limiting example of a physiological dependence. When administered to a mammal, an addictive compound may also create a craving in the mammal for more of it, which is a non-limiting example of a psychological dependence. Examples of addictive compounds include, without limitation, addictive opioids, and the like.

[0221] "Analgesic" and "analgesic agent" refer to a compound that is capable of inhibiting and/or reducing pain in mammals. Pain may be inhibited and/or reduced in the mammal by the binding of the opioid analgesic agent to the mu receptor. When analgesia is effected through the mu receptor, the analgesic agent is referred to as a mu receptor agonist. Certain analgesic agents are capable of inhibiting nociceptive and/or neuropathic pain including, by way of example, morphine, codeine, hydromorphone, oxycodone, hydrocodone, buprenorphin, and the like.

[0222] The term "tolerance" as used herein refers to the psychological and/or physiologic process wherein the patient adjusts to the frequent presence of a substance such that a higher
dose of the substance is required to achieve the same effect. Tolerance may develop at
different times for different effects of the same drug (e.g., analgesic effect versus side
effects). The mechanisms of tolerance are not entirely understood, but they may include
receptor down-regulation or desensitization, inhibitory pathway up-regulation, increased
metabolism, and/or changes in receptor processing (e.g., phosphorylation).

[0223] The therapeutically effective amount of the compound may be higher or lower,
depending on the route of administration used. For example, when direct blood
administration (e.g., sublingual, pulmonary, buccal, or intranasal delivery) is used, a lower
dose of the compound is administered. In one aspect, a therapeutically effective amount of
ibogaine or derivative is from about 50 ng to less than about 100 µg per kg of body weight.
Where other routes of administration are used, a higher dose of the compound is
administered. In one embodiment, the therapeutically effective amount of the compound is
from about 1 mg to about 4 mg per kg of body weight per day.

[0224] The term "dose" refers to a range of ibogaine, ibogaine derivative, or
pharmaceutical salt or solvate thereof that provides a therapeutic serum level of ibogaine
when given to a patient in need thereof. The dose is recited in a range, for example from
about 20 mg to about 120 mg, and can be expressed either as milligrams or as mg/kg body
weight. The attending clinician will select an appropriate dose from the range based on the
patient's weight, age, degree of addiction, health, and other relevant factors, all of which are
well within the skill of the art.

[0225] The term "unit dose" refers to a dose of drug that is given to the patient to provide
therapeutic results, independent of the weight of the patient. In such an instance, the unit dose
is sold in a standard form (e.g., 20 mg tablet). The unit dose may be administered as a single
dose or a series of subdoses. In some embodiments, the unit dose provides a standardized
level of drug to the patient, independent of weight of patient. Many medications are sold
based on a dose that is therapeutic to all patients based on a therapeutic window. In such
cases, it is not necessary to titrate the dosage amount based on the weight of the patient.

Compositions

[0226] As will be apparent to the skilled artisan upon reading this disclosure, in one aspect
this invention provides compositions for treating a disease or disorder as described herein in a
subject, comprising ibogaine. In another aspect this invention further provides compositions
for treating, attenuating, or preventing a disease or disorder or symptoms of a disease or disorder as described herein in a subject, comprising ibogaine.

[0227] This invention is not limited to any particular chemical form of the compounds, and the drug may be given to patients either as a free base, solvate, or as a pharmaceutically acceptable acid addition salt. In the latter case, the hydrochloride salt is generally preferred, but other salts derived from organic or inorganic acids may also be used. Examples of such acids include, without limitation, those described below as "pharmaceutically acceptable salts" and the like.

[0228] In one aspect, the invention provides a pharmaceutical composition comprising a therapeutically or prophylactically effective amount of ibogaine and a pharmaceutically acceptable excipient, wherein the therapeutically or prophylactically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50 ng to less than 10 µg per kg body weight per day. In some aspects, the therapeutically or prophylactically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50 ng to about 10 µg per kg body weight per day.. In some aspects, the composition is formulated for administration once per day. In some aspects, the composition is formulated for administration two or more times per day. Dosing schemes are discussed in further detail below in the subsection titled "Dosing and Routes of Administration."

[0229] In some embodiments, the composition is formulated for sublingual, intranasal, or intrapulmonary delivery. These routes of administration are discussed in further detail below in the subsection titled "Dosing and Routes of Administration."

[0230] In one aspect, the invention provides a pharmaceutical composition comprising a pharmaceutically effective amount of ibogaine, derivative, or salt and/or solvate thereof and a pharmaceutically acceptable excipient, wherein the therapeutically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50 ng to less than 100 µg per kg body weight per day. In some aspects, the therapeutically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50 ng to about 50 µg per kg body weight per day. In some aspects, the therapeutically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50 ng to about 10 µg per kg body weight per day. In some aspects, the therapeutically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50
ng to about 1 µg per kg body weight per day. In some aspects, the composition is formulated for administration once per day. In some aspects, the composition is formulated for administration two or more times per day. The ranges include both extremes as well as any subranges there between.

[0231] In some embodiments, the composition is formulated for oral, transdermal, internal, pulmonary, rectal, nasal, vaginal, lingual, intravenous, intraarterial, intramuscular, intraperitoneal, intracutaneous or subcutaneous delivery. In one embodiment, the therapeutically effective amount of the compound is from about 1 mg to about 8 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.3 mg to about 7 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.3 mg to about 6 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.3 mg to about 5 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.3 mg to about 4 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.3 mg to about 3 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.3 mg to about 2 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.5 mg to about 3 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.7 mg to about 3 mg per kg body weight per day. The ranges include both extremes as well as any subranges there between.

[0232] In one embodiment, the therapeutically effective amount of the compound is about 8 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 7 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 6 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 5 mg/kg body
weight per day. In one embodiment, the therapeutically effective amount of the compound is about 4 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 3 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 2 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 1 mg/kg body weight per day.

[0233] In another aspect, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof and a pharmaceutically acceptable excipient, wherein the therapeutically effective amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is an amount that delivers an aggregate amount of ibogaine of about 50 ng to less than 10 μg per kg body weight per day.

[0234] In one embodiment, the therapeutically effective amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt thereof is an amount that delivers an aggregate amount of ibogaine of about 50 ng to about 1 μg per kg body weight per day.

[0235] In one embodiment, the therapeutically effective amount of the compound is from about 1 mg to about 4 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1 mg to about 3 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1 mg to about 2 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.3 mg to about 3 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.5 mg to about 3 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.7 mg to about 3 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.3 mg to about 4 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 1.5 mg to about 4 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is about 2 mg per kg body weight per day. The ranges include both extremes as well as any subrange or subvalue there between.
In one embodiment, the therapeutically effective amount of the compound is about 4 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 3 mg/kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is about 2 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is about 1.7 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is about 1.5 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is about 1.2 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is about 1 mg per kg body weight per day.

In another aspect, provided herein is a pharmaceutically acceptable formulation comprising a unit dose of ibogaine, wherein the amount of ibogaine is sufficient to provide a serum concentration of about 50 ng/mL to about 500 ng/mL when administered to a patient.

Methods of the Invention

As will be apparent to the skilled artisan upon reading this disclosure, this invention provides a method for treating nicotine addiction, alcohol dependence, drug addiction, pain, depression, impulse control, anxiety, violence/anger, food intake, or tolerance to opioids in a subject, comprising administering to the patient in need thereof a therapeutically effective amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate of each thereof. This invention further provides a method for treating, attenuating, or preventing a disease or disorder or symptoms of a disease or disorder in a subject amenable to treatment with the compounds utilized herein, comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate of each thereof.

Treating Nicotine Addiction

In some embodiments, the invention provides, in certain aspect, a method for treating nicotine addiction in a subject, comprising administering to the patient in need thereof a therapeutically effective amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate of each thereof.
The subject or patient may be any patient who uses nicotine in any form, including cigarettes, electronic cigarettes or vaporizers ("vaping"), chewing tobacco, cigars, snuff, pipes, hookahs, and the like. In some embodiments, the patient is addicted to nicotine. In some embodiments, the patient is physically addicted to nicotine. In some embodiments, the patient is psychologically addicted to nicotine.

In some embodiments, the therapeutically effective amount of the compound is from about 50 ng to less than 10 µg per kilogram body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 50 ng to about 5 µg per kilogram body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 50 ng to about 1 µg per kilogram body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 50 ng to about 1 µg per kilogram body weight per day. In yet another embodiment, the therapeutically effective amount of the compound is from about 500 ng to less than 10 µg per kilogram body weight per day. In yet another embodiment, the therapeutically effective amount of the compound is from about 1 µg to less than 10 µg per kilogram body weight per day. In yet another embodiment, the therapeutically effective amount of the compound may be any amount within any of these ranges, including endpoints.

In some embodiments, the patient is administered periodically, such as once, twice, three times, four times or five times daily with ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the administration is once daily, or once every second day, once every third day, three times a week, twice a week, or once a week. The dosage and frequency of the administration depends on the route of administration, dosage, age and body weight of the patient, condition of the patient, without limitation. Determination of dosage and frequency suitable for the present technology can be readily made a qualified clinician.
[0243] Where the therapeutically effective amount is administered more than one time per day, a portion of the total therapeutically effective amount is administered at each time. For example, an 90 kg patient taking 1 µg ibogaine per kg body weight per day would take 90 µg once a day, 45 µg twice a day, or 30 µg three times a day, etc.

[0244] In some embodiments, the therapeutically effective amount of ibogaine, derivative, or salt and/or solvate thereof is administered once when needed, e.g., when the patient has a craving for nicotine or anticipates to have a craving for nicotine as described herein.

[0245] An ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof, suitable for administration in accordance with the methods provide herein, can be suitable for a variety of delivery modes including, without limitation, oral and transdermal delivery. Compositions suitable for internal, pulmonary, rectal, nasal, vaginal, lingual, intravenous, intra-arterial, intramuscular, intraperitoneal, intracutaneous and subcutaneous routes may also be used. Possible dosage forms include tablets, capsules, pills, powders, aerosols, suppositories, parenterals, and oral liquids, including suspensions, solutions and emulsions. Sustained release dosage forms may also be used. All dosage forms may be prepared using methods that are standard in the art (see e.g., Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton Pa. 1980). In some embodiments, the ibogaine or ibogaine derivative is administered sublingually, intrapulmonarily, or intranasally. These routes of administration are discussed in further detail below in the subsection titled "Dosage and Routes of Administration."

[0246] In a preferred embodiment, ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof is administered orally, which may conveniently be provided in tablet, caplet, sublingual, liquid or capsule form. In certain embodiments, the compound is provided as a pharmaceutically acceptable salt, for example ibogaine HC1, with dosages reported as the amount of free base compound. In some embodiments, the pharmaceutically acceptable salt is provided in hard gelatin capsules containing only the salt with no excipients.

b. Preventing Relapse Of Nicotine Use

[0247] In some embodiments, the invention provides for a method for treating, preventing, or attenuating nicotine cravings in a subject, comprising administering to the patient in need thereof a prophylactically effective amount of ibogaine, an ibogaine derivative, or a
pharmaceutically acceptable salt and/or solvate of each thereof. In some embodiments, the invention provides for a method for preventing recurrence of nicotine addiction in a subject, comprising administering to the patient in need thereof a prophylactically effective amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate of each thereof.

[0248] In some situations, a patient who has not ceased nicotine use nonetheless is unable to use nicotine for an extended amount of time. For example, most airplane flights no longer allow smoking, and have banned vaporizers and e-cigarettes, as well. Other places and situations where nicotine use is not feasible or is difficult include movie theaters, other entertainment venues (including theater, opera, concerts, and the like), and even workplaces, notably hospitals and schools where smoking may not be allowed anywhere on the property. In some embodiments, a prophylactically effective amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered before and/or during a period of time when the patient expects to be unable to use nicotine, wherein the ibogaine, derivative, or salt and/or solvate prevents, interrupts, or attenuates cravings for nicotine. In some embodiments, nicotine cravings are attenuated, interrupted, or prevented for at least 2, 3, 4, 5, 6, 7, 8, 10, 15, or 24 hours.

[0249] In some embodiments, the ibogaine, derivative, or salt and/or solvate is administered on an as-needed basis by the patient. In some embodiments, the ibogaine, derivative, or salt and/or solvate may be administered before the nicotine craving occurs. For example, the patient may take a dose of ibogaine, derivative, or salt and/or solvate in anticipation of cravings, such as before drinking alcohol, before a stressful situation occurs, or when facing another trigger for nicotine use. In some embodiments, the patient takes a dose of ibogaine, derivative, or salt and/or solvate after the nicotine craving occurs, for example during the craving, in order to reduce or eliminate the craving. In some embodiments, the dose of ibogaine, derivative, or salt and/or solvate is low enough that a patient can take one dose before a craving occurs, and another later the same day if he/she feels or anticipates another craving.

[0250] In one embodiment, the prophylactically effective amount of the compound is from about 50 ng to less than 10 µg per kilogram body weight per day. In another embodiment, the prophylactically effective amount of the compound is from about 50 ng to about 1 µg per kilogram body weight per day. In another embodiment, the prophylactically effective amount
of the compound is from about 50 ng to about 500 ng per kilogram body weight per day. In yet another embodiment, the prophylactically effective amount of the compound is from about 50 ng to about 100 µg per kilogram body weight per day. The prophylactically effective amount of the compound may be any amount within any of these ranges, including endpoints.

[0251] In some embodiments, the prophylactically effective amount of ibogaine, derivative, or salt and/or solvate thereof is administered once a day. In some embodiments, the prophylactically effective amount is administered twice per day. In some embodiments, the prophylactically effective amount is administered more than two times per day.

[0252] Where the prophylactically effective amount of ibogaine, derivative, or salt and/or solvate thereof is administered more than one time per day, a portion of the total prophylactically effective amount is administered at each time. For example, an 90 kg patient taking 1 µg ibogaine derivative, or salt and/or solvate per kg body weight per day would take 90 µg once a day, 45 µg twice a day, or 30 µg three times a day, etc.

[0253] In some embodiments, the ibogaine or ibogaine derivative is administered sublingually, intrapulmonary, or intranasally. These routes of administration are discussed in further detail below in the subsection titled "Dosage and Routes of Administration."

c. Alcohol Dependence

[0254] In one aspect, this invention relates to treatment of acute withdrawal from alcohol in an alcohol dependent patient comprising administration of a therapeutically effective amount of ibogaine.

[0255] In one aspect, this invention relates to a method for treating alcohol abuse in an alcohol-dependent patient, comprising administering to the patient a dosage of ibogaine, thereof that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms during said treatment.

[0256] In one aspect, this invention relates to a method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to alcohol dependence, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 60 ng/mL to about 400 ng/mL, said concentration being sufficient to
attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment. In some embodiments, the concentration is sufficient to attenuate said symptoms while maintaining a QT interval of less than about 470 ms during treatment. Preferably, the concentration is sufficient to attenuate said symptoms while maintaining a QT interval of less than about 450 ms during treatment. In one embodiment, the concentration is sufficient to attenuate said symptoms while maintaining a QT interval of less than about 420 ms during treatment. In one embodiment, the withdrawal symptoms are symptoms of acute withdrawal.

[0257] In one aspect, this invention relates to a method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to alcohol dependence, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment. In some embodiments, the concentration is sufficient to attenuate said symptoms while maintaining a QT interval of less than about 470 ms during treatment. Preferably, the concentration is sufficient to attenuate said symptoms while maintaining a QT interval of less than about 450 ms during treatment. In one embodiment, the concentration is sufficient to attenuate said symptoms while maintaining a QT interval of less than about 420 ms during treatment. In one embodiment, the withdrawal symptoms are symptoms of acute withdrawal.

[0258] In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 800 ng/mL or about 60 ng/mL to about 800 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 700 ng/mL or about 60 ng/mL to about 700 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 600 ng/mL, or about 60 ng/mL to about 600 ng/mL. In a preferred embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 500 ng/mL, or about 60 ng/mL to about 500 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 400 ng/mL, or about 60 ng/mL to about 400 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 300 ng/mL, or about 60 ng/mL to about 300 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 200 ng/mL, or about 60 ng/mL to about 200 ng/mL. In one
embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 100 ng/mL, or about 60 ng/mL to about 100 ng/mL. The ranges include both extremes as well as any subranges between.

[0259] In some embodiments, the patient is administered periodically, such as once, twice, three times, four times or five times daily with ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the administration is once daily, or once every second day, once every third day, three times a week, twice a week, or once a week. The dosage and frequency of the administration depends on the route of administration, dosage, age and body weight of the patient, condition of the patient, without limitation. Determination of dosage and frequency suitable for the present technology can be readily made a qualified clinician.

[0260] In some embodiments, the ibogaine or ibogaine derivative is administered sublingually, intrapulmonary, or intranasally. These routes of administration are discussed in further detail below in the subsection titled "Dosage and Routes of Administration."

[0261] In some embodiments, the therapeutically effective amount of ibogaine is administered orally, which may conveniently be provided in tablet, caplet, sublingual, liquid or capsule form. In certain embodiments, the ibogaine is provided as ibogaine HC1, with dosages reported as the amount of free base ibogaine. In some embodiments, the ibogaine HC1 is provided in hard gelatin capsules containing only ibogaine HC1 with no excipients.

[0262] In one aspect, this invention relates to treatment or attenuation of post-acute withdrawal from alcohol dependence, and/or symptoms of withdrawal, in an addicted patient by administering a maintenance amount of ibogaine. In some aspects, this invention relates to a method to prevent relapse of alcohol abuse and/or use in an addicted patient treated to ameliorate said abuse, said method comprising periodically administering to said patient a maintenance dosage of ibogaine.

[0263] These dosing amounts, including administration of a maintenance amount of ibogaine, are discussed in further detail below in the subsection titled "Dosage and Routes of Administration."
d. Drug Addiction

[0264] In some aspects, the present invention provides a method for treating substance abuse or addiction, including acute and post-acute withdrawal symptoms, in an addicted patient, comprising administering to the patient a dosage of ibogaine.

[0265] In one aspect, this invention relates to treatment of acute withdrawal from an addictive substance in an addicted patient comprising administration of a therapeutically effective amount of ibogaine.

[0266] In one aspect, this invention relates to a method for treating substance abuse in an addicted patient, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms during said treatment.

[0267] In one aspect, this invention relates to a method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to substance addiction, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

[0268] In one aspect, this invention relates to a method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to substance addiction, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

[0269] In some embodiments, the therapeutic dose of ibogaine is a tapered dosing over a period of time, during which the patient is detoxified, for example, without suffering significant acute withdrawal symptoms. Without being bound by theory, it is believed that tapering will allow the full therapeutic effect of the compound with less prolongation of the QT interval. Tapering involves administration of one or more subsequently lower doses of the compound over time.
In one aspect, this invention relates to treatment or attenuation of post-acute withdrawal from an addictive substance in an addicted patient with a maintenance amount of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof.

In some aspects, this invention relates to a method to prevent relapse of substance abuse in an addicted patient treated to ameliorate said abuse, said method comprising periodically administering to said patient a maintenance dosage of ibogaine.

In some embodiments, the patient undergoes long-term (e.g., one year or longer) treatment with maintenance doses of ibogaine. In some embodiments, the patient is treated for acute withdrawal with therapeutic doses of ibogaine and then the amount of compound is reduced to maintenance levels after acute withdrawal symptoms would be expected to have subsided. Acute withdrawal symptoms generally are the most pronounced in the first 48 to 72 hours after cessation of the drug of addiction, although acute withdrawal may last as long as a week or more.

e. Pain

In one aspect, this invention relates to treatment of pain in a patient suffering from pain comprising administration of a therapeutically effective amount of ibogaine.

In one aspect, this invention relates to a method for treating pain in a patient suffering from pain, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL, said concentration being sufficient to inhibit or ameliorate said pain. In one embodiment, the dosage of ibogaine results in prolongation of the QT interval of less than about 50 ms. In one embodiment, the dosage of ibogaine results in a QT interval of less than about 500 ms.

In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 800 ng/mL or about 20 ng/mL to about 800 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 700 ng/mL or about 20 ng/mL to about 700 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 600 ng/mL, or about 20ng/mL to about 600 ng/mL. In a preferred embodiment, the average serum concentration of is from about 50 ng/mL to about 500 ng/mL, or about 20ng/mL to about 500 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 400 ng/mL, or about 20ng/mL to about 400 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 300 ng/mL, or about 20ng/mL to about 300 ng/mL.
In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 200 ng/mL, or about 20ng/mL to about 200 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 100 ng/mL, or about 20ng/mL to about 100 ng/mL. The ranges include both extremes as well as any subranges between.

[0276] In one embodiment, the dosage or aggregate dosage of ibogaine is from greater than about 1 mg/kg to about 8 mg/kg body weight per day.

f. Depression

[0277] The following description of depressive disorders and PTSD is provided for the purpose of facilitating an understanding of the utility of the compounds and compositions of this invention. The definitions of depressive disorders and PTSD given below are those listed in American Psychiatric Association, 1994a or American Psychiatric Association, 1987. Additional information regarding these disorders can be found in this reference, as well as other references cited below, all of which are hereby incorporated herein by reference.

[0278] In some embodiments, it is contemplated that the compounds of this invention will be effective in treating depression in patients who have been diagnosed as having depression based upon the administration of any of the following tests: Hamilton Depression Rating Scale (HDRS), Hamilton depressed mood item, Clinical Global Impressions (CGI)-Severity of Illness. It is further contemplated that the compounds of the invention will be effective in improving certain of the factors measured in these tests, such as the HDRS subfactor scores, including the depressed mood item, sleep disturbance factor and anxiety factor, and the CGI-Severity of Illness rating. It is also contemplated that the compounds of this invention will be effective in preventing relapse of major depressive episodes.

[0279] This invention provides, in certain embodiments, a method of treating a patient suffering from major depressive disorder, which comprises administering to the patient a therapeutically effective amount of any of the compounds utilized herein effective to treat the subject's major depressive disorder.

[0280] The invention also provides a method of treating a patient suffering from dysthymic disorder, bipolar I or II disorder, schizoaffective disorder, a cognitive disorder with depressed mood, a personality disorder, insomnia, hypersonmia, narcolepsy, circadian rhythm sleep disorder, nightmare disorder, sleep terror disorder or sleepwalking disorder.
It is contemplated that the compounds utilized herein can be effective in treating PTSD in patients who have been diagnosed as having PTSD based upon the administration of any of the following tests: Clinician-Administered PTSD Scale Part 2 (CAPS), the patient-rated Impact of Event Scale (IES). It is further contemplated that the compounds described herein will be effective in inducing improvements in the scores of the CAPS, IES, CGI-Severity of Illness or CGI-Global Improvement tests. It is also contemplated that the compounds described herein will be effective in preventing relapse of PTSD.

This invention provides a method of treating post-traumatic stress disorder in a subject, which comprises administering to the patient a therapeutically effective amount of any of the compounds utilized herein to treat the subject's post-traumatic stress disorder.

Another aspect of the current invention provides a method for treating depression and/or PTSD in a patient in need thereof, which method comprises administering ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof to the patient, wherein the amount of the ibogaine or ibogaine derivative is sufficient to treat depression and/or PTSD in the patient.

In a preferred embodiment, the invention provides a method for treating depression and/or posttraumatic stress disorder 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, wherein the patient is not addicted to cocaine or an opiate, and further wherein the therapeutically effective amount provides average ibogaine or ibogaine derivative serum levels of between about 50 to about 800 ng/ml. In some embodiments, the average ibogaine or ibogaine derivative serum level provided by the dosage is less than about 50 ng/mL. In one embodiment, the therapeutically effective amount is between about 1 mg to about 8 mg per kg of body weight. In one embodiment, the therapeutically effective amount is between about 50 ng to less than 100 µg per kg of body weight. In one embodiment, depression is treated. In one embodiment, posttraumatic stress disorder is treated. In one embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered by sublingual, intranasal, or intrapulmonary delivery.
g. Reduced Tolerance To Opioid Analgesics

[0285] As will be apparent to the skilled artisan upon reading this disclosure, the present invention provides a method for modulating tolerance to opioids in a patient undergoing opioid analgesic therapy, comprising administering to the patient a dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof.

[0286] In one aspect of this invention, patient is being treated with an addictive opioid analgesic to relieve the patient's pain. The pain may be of any type and from any source. In one embodiment, the patient is treated for acute pain. In one embodiment, the patient is treated for chronic pain. In one embodiment, the patient is treated for nociceptive pain. In one embodiment, the patient is treated for neuropathic pain. In some embodiments, the pain is caused by surgery, diabetes, trigeminal neuralgia, fibromyalgia, cancer, central pain syndrome, tissue damage, physical injury, and the like. In some embodiments, the source of the pain is unknown or unclear.

[0287] In one aspect, this invention relates to a method for modulating tolerance to an opioid analgesic in a patient undergoing opioid analgesic therapy, the method comprising interrupting or administering concurrently with said opioid analgesic an amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL, said concentration being sufficient to resensitize the patient to the opioid as an analgesic while maintaining a QT interval of less than about 500 ms during said treatment.

[0288] In one aspect, this invention relates to a method for modulating tolerance to an opioid analgesic in a patient undergoing opioid analgesic therapy, the method comprising interrupting or administering concurrently with said opioid analgesic an amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 60 ng/mL to about 400 ng/mL, said concentration being sufficient to resensitize the patient to the opioid as an analgesic while maintaining a QT interval of less than about 500 ms during said treatment. In some embodiments, the concentration is sufficient to resensitize the patient to the opioid as an analgesic while maintaining a QT interval of less than about 470 ms during treatment. Preferably, the concentration is sufficient to resensitize the patient to the opioid as an analgesic while maintaining a QT interval of less than about 450 ms during treatment. In one embodiment,
the concentration is sufficient to resensitize the patient to the opioid as an analgesic while maintaining a QT interval of less than about 420 ms during treatment.

[0289] In some embodiments, the patient is administered periodically, such as once, twice, three times, four times or five times daily with ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the administration is once daily, or once every second day, once every third day, three times a week, twice a week, or once a week. The dosage and frequency of the administration depends on the route of administration, dosage, age and body weight of the patient, condition of the patient, opioid analgesic to which tolerance is being modulated, length of time of analgesic treatment, and the like, without limitation. Determination of dosage and frequency suitable for the present technology can be readily made a qualified clinician.

[0290] The patient may be receiving any addictive opioid analgesic for the treatment of pain. In a preferred embodiment, the opioid analgesic is selected from the group consisting of fentanyl, hydromorphone, morphine, oxycodone, buprenorphine, codeine, heroin, thebaine, buprenorphine, methadone, meperidine, tramadol, tapentadol, levorphanol, sufentanil, pentazocine, oxymorphone, and derivatives of each thereof.

h. Impulse Control Disorder, Anxiety-Related Disorders, Violence And/Or Anger, or Regulating Food Intake

[0291] As will be apparent to the skilled artisan upon reading this disclosure, this invention provides a method for treating anxiety disorder, impulse control disorder, anger/violence-related disorders, or regulating food intake in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of ibogaine, an ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof. In a preferred embodiment, the patient is not addicted to cocaine or an opiate.

[0292] The following description of anxiety disorders and impulse control disorders is provided for the purpose of facilitating an understanding of the utility of the compounds and compositions of this invention. Disorders associated with violence and/or anger are included in these descriptions. The definitions of anxiety disorders and impulse control disorders given below are those listed in American Psychiatric Association, 2013, American Psychiatric Association, 1994a, or American Psychiatric Association, 1987. Additional information regarding these disorders can be found in these references, as well as other references cited below, all of which are hereby incorporated herein by reference.
Anxiety disorders include panic disorder, agoraphobia with or without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder and generalized anxiety disorder. It is contemplated that the compounds of this invention will be effective in treating these disorders in patients who have been diagnosed as having such disorders.

This invention provides a method of treating a patient suffering from anxiety which comprises administering to the patient an amount of any of the compounds described herein effective to treat the subject's anxiety.

It is contemplated that the compounds described herein will be effective in treating obsessions and compulsions in patients who have been diagnosed as having obsessive compulsive disorder based upon administration of appropriate tests, which may include, but are not limited to any of the following: Yale Brown Obsessive Compulsive Scale (YBOCS) (for adults), National Institute of Mental Health Global OCD Scale (NIMH GOCS), CGI-Severity of Illness scale. It is further contemplated that the compounds described herein will be effective in inducing improvements in certain of the factors measured in these tests, such as a reduction of several points in the YBOCS total score. It is also contemplated that the compounds described herein will be effective in preventing relapse of obsessive compulsive disorder and/or symptoms thereof.

This invention provides a method of treating obsessions and/or compulsions in a patient with obsessive compulsive disorder, which comprises administering to the patient a therapeutically effective amount of any of the compounds utilized herein effective to treat the subject's obsessions and/or compulsions.

It is contemplated that the compounds described herein will be effective in treating panic disorder in patients who have been diagnosed with panic disorder on the basis of frequency of occurrence of panic attacks, or by means of the CGI-Severity of Illness scale. It is further contemplated that the compounds described herein will be effective in inducing improvements in certain of the factors measured in these evaluations, such as a reduction in frequency or elimination of panic attacks, an improvement in the CGI-Severity of Illness scale or a CGI-Global Improvement score of 1 (very much improved), 2 (much improved) or 3 (minimally improved). It is also contemplated that the compounds described herein will be effective in preventing relapse of panic disorder.
This invention provides a method of treating panic disorder, with or without agoraphobia, in a subject, which comprises administering to the patient a therapeutically effective amount of any of the compounds utilized herein to treat the subject's panic disorder.

It is contemplated that the compounds described herein can be effective in treating social anxiety disorder in patients who have been diagnosed as having social anxiety disorder based upon the administration of any of the following tests: the Liebowitz Social Anxiety Scale (LSAS), the CGI-Severity of Illness scale, the Hamilton Rating Scale for Anxiety (HAM-A), the Hamilton Rating Scale for Depression (HAM-D), the axis V Social and Occupational Functioning Assessment Scale of DSM-IV, the axis II (ICD-10) World Health Organization Disability Assessment, Schedule 2 (DAS-2), the Sheehan Disability Scales, the Schneier Disability Profile, the World Health Organization Quality of Life- 100 (WHOQOL-100), or other tests as described in Bobes, 1998, which is incorporated herein by reference. It is further contemplated that the compounds described herein will be effective in inducing improvements as measured by these tests, such as the a change from baseline in the Liebowitz Social Anxiety Scale (LSAS), or a CGI-Global Improvement score of 1 (very much improved), 2 (much improved) or 3 (minimally improved). It is also contemplated that the compounds described herein will be effective in preventing relapse of social anxiety disorder.

This invention provides a method of treating social anxiety disorder in a patient which comprises administering to the patient a therapeutically effective amount of any of the compounds utilized herein to treat the subject's social anxiety disorder.

It is contemplated that the compounds utilized herein can be effective in treating generalized anxiety disorder in patients who have been diagnosed as having this disorder based upon the diagnostic criteria described in DSM-IV or DSM-5. It is further contemplated that the compounds utilized herein will be effective in reducing symptoms of this disorder, such as the following: excessive worry and anxiety, difficulty controlling worry, restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, or sleep disturbance. It is also contemplated that the compounds described herein will be effective in preventing relapse of general anxiety disorder.
The invention provides a method of treating generalized anxiety disorder in a subject, which comprises administering to the patient an amount of any of the compounds described herein effective to treat the subject's generalized anxiety disorder.

Impulse control disorders include pathological gambling (PG), kleptomania, trichotillomania (TTM), intermittent explosive disorder (IED), and pyromania. Impulse control disorders may also include pathological skin picking (PSP), compulsive sexual behavior (CSB), compulsive buying (CB), conduct disorder, antisocial personality disorder, oppositional defiant disorder, borderline personality disorder, attention deficit/hyperactivity disorder (ADHD, which includes attention deficit disorder, ADD), schizophrenia, mood disorders, paraphilia, and internet addiction. Symptoms of impulse control disorders include: repetitive participation in behavior despite adverse consequences, diminished control over the behavior, an urge/impulse to engage in the behavior, and feelings of pleasure while participating in the behavior.

It is contemplated that the compounds utilized herein can be effective in treating impulse control disorders in patients who have at least one impulse control disorder based upon the diagnostic criteria described in DSM-IV or DSM-5. It is further contemplated that the compounds utilized herein will be effective in reducing symptoms of this disorder, including impulsivity or lack of self-control. It is also contemplated that the compounds described herein will be effective in preventing relapse of the impulse control disorder.

It is contemplated that the compounds utilized herein can be effective in treating ADHD or ADD in patients who have the disorder, based upon the diagnostic criteria described in DSM-IV or DSM-5. It is further contemplated that the compounds utilized herein will be effective in reducing symptoms of this disorder, including impulsivity or lack of self-control. It is also contemplated that the compounds described herein will be effective in preventing relapse of ADD or ADHD.

It is contemplated that the compounds utilized herein can be effective in treating schizophrenia in patients who have the disorder, based upon the diagnostic criteria described in DSM-IV or DSM-5. Schizophrenia is characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction. It is further contemplated that the compounds utilized herein will be effective in
reducing symptoms of this disorder. It is also contemplated that the compounds described herein will be effective in preventing relapse of schizophrenia.

[0307] It is contemplated that the compounds described herein will be effective in treating non-suicidal self injury disorder in patients who have been diagnosed with this disorder based on the patient's exhibition of symptoms including deliberate tissue injury without suicidal intent (e.g., cutting, burning, self-poisoning, or self-mutilation). It is further contemplated that the compounds described herein will be effective in inducing improvements in certain of these factors, such as a reduction in frequency or elimination of self injury. It is also contemplated that the compounds described herein will be effective in preventing relapse of non-suicidal self injury disorder.

[0308] This invention provides a method of treating non-suicidal self injury disorder in a subject, which comprises administering to the patient a therapeutically effective amount of any of the compounds utilized herein to treat the subject's non-suicidal self injury disorder.

[0309] It is contemplated that the compounds described herein will be effective in treating Munchausen syndrome in patients who have been diagnosed with this disorder based on the patient's propensity for feigning disease, illness, or psychological trauma to draw attention, sympathy, or reassurance to themselves. Symptoms may include frequent hospitalizations, knowledge of several illnesses, frequent requests for medication (e.g., pain killers), willingness to undergo extensive surgery, few to no visitors during hospitalizations, and exaggerated or fabricated stories about multiple medical problems. It is further contemplated that the compounds described herein will be effective in inducing improvements in certain of these factors, such as a reduction in frequency or elimination of one or more symptoms. It is also contemplated that the compounds described herein will be effective in preventing relapse of Munchausen syndrome. Munchausen syndrome also includes Munchausen syndrome by proxy, in which a caregiver exaggerates, fabricates, or induces illness in someone in his/her care.

[0310] This invention provides a method of treating Munchausen syndrome in a subject, which comprises administering to the patient a therapeutically effective amount of any of the compounds utilized herein to treat the subject's Munchausen syndrome.

[0311] It is contemplated that the compounds described herein will be effective in treating disruptive mood dysregulation disorder in patients who have been diagnosed with this
disorder on the basis of severe and recurrent temper outbursts, grossly out of proportion to the stimulus or situation, as well as a persistent irritable/angry mood most of the time. It is further contemplated that the compounds described herein will be effective in inducing improvements in certain of these factors, such as a reduction in frequency or elimination of temper outbursts and/or an improvement in mood. It is also contemplated that the compounds described herein will be effective in preventing relapse of disruptive mood dysregulation disorder.

[0312] This invention provides a method of treating disruptive mood dysregulation disorder in a subject, which comprises administering to the patient a therapeutically effective amount of any of the compounds utilized herein to treat the subject's disruptive mood dysregulation disorder.

[0313] It is contemplated that the compounds utilized herein can be effective in reducing the frequency, intensity, and duration of anger and/or violence in individuals prone to one or both. Although anger and violence disorders other than those associated with other disorders (e.g., as described above) are not outlined in DSM IV or DSM 5, many health professionals recognize that such disorders are associated with significant dysfunction. Anger management training and other psychosocial treatments are often used in an effort to treat these individuals.

[0314] This invention provides a method of treating anger- and/or violence-related disorder in a subject, which comprises administering to the patient a therapeutically effective amount of any of the compounds utilized herein to treat the subject's anger- and/or violence-related disorder.

[0315] It is contemplated that the compounds utilized herein can be effective in regulating food intake and/or reducing food cravings in patients in need thereof. In some embodiments, the patient is overweight. In some embodiments, the patient is obese. In some embodiments, the patient exhibits comorbidities associated with overweight/obesity, for example coronary heart disease, high blood pressure, stroke, type 2 diabetes, abnormal levels of blood fats, metabolic syndrome, cancer, osteoarthritis, sleep apnea, reproductive issues, and/or gallstones.

[0316] This invention provides a method of regulating food intake and/or reducing food cravings in a subject, which comprises administering to the patient a therapeutically effective
amount of any of the compounds utilized herein to regulate/reduce the subject's food intake and/or food cravings.

[0317] In a preferred embodiment, the invention provides a method for treating anxiety disorders, impulse control disorders, OCD, and/or anger/violence-related disorders, or regulating food intake and/or food cravings, 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, wherein the patient is not addicted to cocaine or an opiate, and further wherein the therapeutically effective amount provides average ibogaine serum levels of between about 50 to about 180 ng/ml. In some embodiments, the average ibogaine serum level provided by the dosage is less than about 50 ng/mL. In one embodiment, the therapeutically effective amount is between about 1 mg to about 4 mg per kg of body weight. In one embodiment, the therapeutically effective amount is between about 50 ng to about 100 µg per kg of body weight. In one embodiment, an anxiety disorder is treated. In one embodiment, OCD is treated. In one embodiment, an impulse control disorder is treated. On one embodiment, an anger-related disorder is treated, in one embodiment, a violence-related disorder is treated. In one embodiment, symptoms of anger are reduced or eliminated. In one embodiment, violent outbursts are reduced or eliminated. In one embodiment, food intake is regulated. In one embodiment, food cravings are attenuated. In one embodiment, the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered by sublingual, buccal, intranasal, or intrapulmonary delivery.

[0318] In one aspect, this invention relates to a method for attenuating symptoms of anxiety disorder, impulse control disorder, or an anger and/or violence-related disorder in a human patient, comprising administering to the patient a dosage of ibogaine or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 180 ng/mL, said concentration being sufficient to attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

[0319] In one aspect, this invention relates to a method for attenuating food cravings in a human patient, comprising administering to the patient a dosage of ibogaine or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 250 ng/mL, said concentration being sufficient to attenuate said cravings while maintaining a QT interval of less than about 500 ms during said
treatment. In some embodiments, the concentration is sufficient to attenuate said cravings while maintaining a QT interval of less than about 470 ms during treatment. Preferably, the concentration is sufficient to attenuate said cravings while maintaining a QT interval of less than about 450 ms during treatment. In one embodiment, the concentration is sufficient to attenuate said cravings while maintaining a QT interval of less than about 420 ms during treatment.

[0320] In one embodiment, the QT interval is not prolonged more than about 50 ms. In one embodiment, the QT interval is not prolonged more than about 40 ms. In one embodiment, the QT interval is not prolonged more than about 30 ms. In a preferred embodiment, the QT interval is not prolonged more than about 20 ms. In one embodiment, the QT interval is not prolonged more than about 10 ms.

[0321] In one aspect, this invention relates to a method for treating an anxiety disorder, an impulse control disorder, or an anger/violence-related disorder, and/or treating or attenuating the symptoms thereof in a patient, comprising selecting a patient exhibiting symptoms of an anxiety disorder, impulse control disorder, or anger/violence-related disorder who is prescreened to evaluate the patient's expected tolerance for prolongation of QT interval, administering to the patient a dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to inhibit or ameliorate said disorder or symptoms while maintaining a QT interval of less than about 500 ms during said treatment. In some embodiments, the concentration is sufficient to attenuate said symptoms while maintaining a QT interval of less than about 470 ms during treatment. Preferably, the concentration is sufficient to attenuate said symptoms while maintaining a QT interval of less than about 450 ms during treatment. In one embodiment, the concentration is sufficient to attenuate said symptoms while maintaining a QT interval of less than about 420 ms during treatment.

[0322] In one aspect, this invention relates to a method for regulating food intake, and/or treating or attenuating food cravings, in a patient, comprising selecting an overweight or obese patient who is prescreened to evaluate the patient's expected tolerance for prolongation of QT interval, administering to the patient a dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 180 ng/mL, said concentration being sufficient to
inhibit or ameliorate said disorder or symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

IV. Dosage and Routes of Administration

Therapeutic Dose

[0323] In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 800 ng/mL or about 60 ng/mL to about 800 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 700 ng/mL or about 60 ng/mL to about 700 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 600 ng/mL, or about 60 ng/mL to about 600 ng/mL. In a preferred embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 500 ng/mL, or about 60 ng/mL to about 500 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 400 ng/mL, or about 60 ng/mL to about 400 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 300 ng/mL, or about 60 ng/mL to about 300 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 200 ng/mL, or about 60 ng/mL to about 200 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 100 ng/mL, or about 60 ng/mL to about 100 ng/mL. The ranges include both extremes as well as any subranges between.

[0324] In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 180 ng/mL, or about 60 ng/mL to about 180 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 150 ng/mL, or about 60 ng/mL to about 150 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 50 ng/mL to about 100 ng/mL, or about 60 ng/mL to about 100 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 80 ng/mL to about 150 ng/mL. In one embodiment, the average serum concentration of ibogaine is from about 80 ng/mL to about 100 ng/mL. The ranges include both extremes as well as any subrange or subvalue there between.

[0325] In one embodiment, the dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a serum concentration of between about 1000 ng/hr/mL and about 6000 ng/hr/mL. In one embodiment, the dosage of
ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a serum concentration of between about 1200 ng*hr/mL and about 5800 ng*hr/mL. In one embodiment, the dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a serum concentration of between about 1200 ng*hr/mL and about 5500 ng*hr/mL. The ranges include both extremes as well as any subrange or subvalue there between.

[0326] In one embodiment, the dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a maximum serum concentration (Cmax) of less than about 250 ng/mL. In one embodiment, the dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a Cmax between about 40 ng/mL and about 250 ng/mL. In a preferred embodiment, the dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a Cmax between about 60 ng/mL and about 200 ng/mL. In one embodiment, the dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a Cmax between about 100 ng/mL and about 180 ng/mL. The ranges include both extremes as well as any subrange or subvalue there between.

[0327] In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from greater than about 1 mg/kg to about 8 mg/kg body weight per day. The aggregate dosage is the combined dosage, for example the total amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof administered over a 24-hour period where smaller amounts are administered more than once per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is from about 1.3 mg/kg to about 7 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is from about 1.3 mg/kg to about 6 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is from about 1.3 mg/kg to about 5 mg/kg body weight. In a preferred embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is from about 1.3 mg/kg to about 4 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is from about 1.3 mg/kg to about 3 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative,
or salt and/or solvate thereof is from about 1.3 mg/kg to about 2 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is from about 1.5 mg/kg to about 3 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is from about 1.7 mg/kg to about 3 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is from about 2 mg/kg to about 4 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is from about 2 mg/kg to about 3 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 2 mg/kg body weight. The ranges include both extremes as well as any subranges there between.

[0328] In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 8 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 7 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 6 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 5 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 4 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 3 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 2 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 1.7 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 1.5 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 1.3 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt and/or solvate thereof is about 1 mg/kg body weight per day.

[0329] In one aspect, the invention provides administering a pharmaceutical composition comprising a pharmaceutically effective amount of ibogaine and a pharmaceutically
acceptable excipient, wherein the therapeutically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50 ng to about 100 µg per kg body weight per day. In some aspects, the therapeutically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50 ng to about 50 µg per kg body weight per day. In some aspects, the therapeutically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50 ng to about 10 µg per kg body weight per day. In some aspects, the therapeutically effective amount of ibogaine is an amount that delivers an aggregate amount of ibogaine of about 50 ng to about 1 µg per kg body weight per day. In some aspects, the composition is administered once per day. In some aspects, the composition is administered less than once a day, for example once every two days, once every three days, once every four days, once a week, etc.

[0330] In one embodiment, the dosage or aggregate dosage of compound is from about 1 mg to about 4 mg per kg body weight per day. The aggregate dosage is the combined dosage, for example the total amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof administered over a 24-hour period where smaller amounts are administered more than once per day.

[0331] In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt or solvate thereof is between about 70 mg and about 150 mg. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt or solvate thereof is between about 75 mg and about 150 mg. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt or solvate thereof is between about 80 mg and about 140 mg. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt or solvate thereof is between about 90 mg and about 140 mg. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt or solvate thereof is between about 90 mg and about 130 mg. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt or solvate thereof is between about 100 mg and about 130 mg. In one embodiment, the dosage or aggregate dosage of ibogaine, ibogaine derivative, or salt or solvate thereof is between about 110 mg and about 130 mg. The ranges include both extremes as well as any subrange or subvalue there between.

[0332] In another embodiment, there is provided a unit dose of ibogaine, ibogaine derivative, or salt or solvate thereof which is about 50 mg to about 200 mg per dose. In one
embodiment, the unit dose is about 50 to about 120 mg per dose. In one embodiment, the unit dose is about 120 mg per dose. It being understood that the term "unit dose" means a dose sufficient to provide therapeutic results whether given all at once or serially over a period of time.

[0333] In some embodiments, the patient is administered an initial dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt or solvate thereof, followed by one or more additional doses. In one embodiment, such a dosing regimen provides an average serum concentration of ibogaine of about 50 ng/mL to about 180 ng/mL. In one embodiment, the one or more additional doses maintain an average serum concentration of about 50 ng/mL to about 180 ng/mL over a period of time.

[0334] In some embodiments, the initial dose of ibogaine, ibogaine derivative, or salt or solvate thereof is from about 75 mg to about 120 mg. In one embodiment, the initial dose is about 75 mg. In one embodiment, the initial dose is about 80 mg. In one embodiment, the initial dose is about 85 mg. In one embodiment, the initial dose is about 90 mg. In one embodiment, the initial dose is about 95 mg. In one embodiment, the initial dose is about 100 mg. In one embodiment, the initial dose is about 105 mg. In one embodiment, the initial dose is about 110 mg. In one embodiment, the initial dose is about 115 mg. In one embodiment, the initial dose is about 120 mg.

[0335] In some embodiments, the one or more additional doses are lower than the initial dose. In one embodiment, the one or more additional doses are from about 5 mg to about 50 mg. In one embodiment, the one or more additional doses may or may not comprise the same amount of ibogaine, ibogaine derivative, or salt or solvate thereof. In one embodiment, at least one additional dose is about 5 mg. In one embodiment, at least one additional dose is about 10 mg. In one embodiment, at least one additional dose is about 15 mg. In one embodiment, at least one additional dose is about 20 mg. In one embodiment, at least one additional dose is about 25 mg. In one embodiment, at least one additional dose is about 30 mg. In one embodiment, at least one additional dose is about 35 mg. In one embodiment, at least one additional dose is about 40 mg. In one embodiment, at least one additional dose is about 45 mg. In one embodiment, at least one additional dose is about 50 mg.

[0336] In one embodiment, the one or more additional doses are administered periodically. In one embodiment, the one or more additional doses are administered approximately every 4
hours. In one embodiment, the one or more additional doses are administered every 6 hours. In one embodiment, the one or more additional doses are administered approximately every 8 hours. In one embodiment, the one or more additional doses are administered approximately every 10 hours. In one embodiment, the one or more additional doses are administered approximately every 12 hours. In one embodiment, the one or more additional doses are administered approximately every 18 hours. In one embodiment, the one or more additional doses are administered approximately every 24 hours. In one embodiment, the one or more additional doses are administered approximately every 36 hours. In one embodiment, the one or more additional doses are administered approximately every 48 hours.

[0337] In some embodiments, the patient is administered a high (therapeutic) dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof for a period of time to ameliorate the most significant symptoms of a disease or disorder, and then is administered a lower (maintenance) dose to prevent relapse. In some embodiments, the patient is administered a therapeutic dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof for a period of time to ameliorate the most significant symptoms, and then is administered a decreasing (tapered) amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof over time until the maintenance dose is reached.

[0338] For treating pain the following dosages are contemplated as useful.

[0339] In one embodiment, the therapeutically effective amount of the compound is from about 0.1 mg to about 5 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.1 mg to about 3 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.1 mg to about 2 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.1 mg to about 1.5 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.1 mg to about 1 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.5 mg to about 3 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.5 mg to about 2 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.5 mg to about 1.5 mg per kg body weight per day. In another
embodiment, the therapeutically effective amount of the compound is from about 0.5 mg to about 1.3 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.5 mg to about 1.2 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.5 mg to about 1.1 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.5 mg to about 1 mg per kg body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 0.7 mg to about 1.5 mg per kg body weight per day. The ranges include both extremes as well as any subranges there between.

[0340] In one embodiment, the therapeutically effective amount of the compound is about 3 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 2 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 1.5 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 1.4 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 1.3 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 1.2 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 1.1 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 1 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 0.9 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 0.8 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 0.7 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 0.6 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 0.5 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 0.4 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 0.3 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 0.2 mg/kg body weight per day. In one embodiment, the therapeutically effective amount of the compound is about 0.1 mg/kg body weight per day.

[0341] In one embodiment, Ibogaine is administered at an amount by weight that is twice that administered for noribogaine for treating a same or similar condition. For example, and
without limitation, an administration of a dose 80 mg ibogaine approximates a dose of 40 mg noribogaine.

**Maintenance Dose**

[0342] In some embodiments, the maintenance dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is about 10% to about 80% of the therapeutic dose. In some embodiments, the maintenance dose of ibogaine or pharmaceutically acceptable salt and/or solvate thereof is about 70% of the therapeutic dose. In some embodiments, the maintenance dose is about 60% of the therapeutic dose. In some embodiments, the maintenance dose is about 50% of the therapeutic dose. In some embodiments, the maintenance dose is about 40% of the therapeutic dose. In some embodiments, the maintenance dose is about 30% of the therapeutic dose. In some embodiments, the maintenance dose is about 20% of the therapeutic dose. In some embodiments, the maintenance dose is about 10% of the therapeutic dose.

[0343] In some embodiments, the maintenance average serum level of ibogaine is about 10% to about 80% of the therapeutic average serum level of ibogaine. In some embodiments, the maintenance average serum level of ibogaine is about 70% of the therapeutic average serum level of ibogaine. In some embodiments, the maintenance average serum level of ibogaine is about 60% of the therapeutic average serum level of ibogaine. In some embodiments, the maintenance average serum level of ibogaine is about 50% of the therapeutic average serum level of ibogaine. In some embodiments, the maintenance average serum level of ibogaine is about 40% of the therapeutic average serum level of ibogaine. In some embodiments, the maintenance average serum level of ibogaine is about 30% of the therapeutic average serum level of ibogaine. In some embodiments, the maintenance average serum level of ibogaine is about 20% of the therapeutic average serum level of ibogaine. In some embodiments, the maintenance average serum level of ibogaine is about 10% of the therapeutic average serum level of ibogaine.

**Tapered Dosing**

[0344] In some embodiments, the therapeutic dose of ibogaine, ibogaine derivative, or salt and/or solvate thereof is a tapered dosing over a period of time, during which the patient is detoxified, for example, without suffering significant acute withdrawal symptoms. Without being bound by theory, it is believed that tapering will allow the full therapeutic effect of
ibogaine with less prolongation of the QT interval. Tapering involves administration of one or more subsequently lower doses of ibogaine over time. For example, in some embodiments, the first tapered dose is about 50% to about 95% of the first or original dose. In some embodiments, the second tapered dose is about 40% to about 90% of the first or original dose. In some embodiments, the third tapered dose is about 30% to about 85% of the first or original dose. In some embodiments, the fourth tapered dose is about 20% to about 80% of the first or original dose. In some embodiments, the fifth tapered dose is about 10% to about 75% of the first or original dose.

[0345] In some embodiments, the first tapered dose is given after the first dose of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the first tapered dose is given after the second, third, or a subsequent dose of compound. The first tapered dose may be administered at any time after the previous dose of compound.

[0346] In one embodiment, the therapeutic dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate is tapered over time until the desired maintenance dose is reached. For example, in some embodiments, the first tapered dose is about 50%, to about 95% of the therapeutic dose. In some embodiments, the second tapered dose is about 40% to about 90% of the therapeutic dose. In some embodiments, the third tapered dose is about 30% to about 85% of the therapeutic dose. In some embodiments, the fourth tapered dose is about 20% to about 80% of the therapeutic dose. In some embodiments, the fifth tapered dose is about 10% to about 75% of the therapeutic dose. In some embodiments, one tapered dose is given to achieve the maintenance dose. In some embodiments, two tapered doses are given to achieve the maintenance dose. In some embodiments, three tapered doses are given to achieve the maintenance dose. In some embodiments, four or more tapered doses are given to achieve the maintenance dose. Determination of the tapered doses, number of tapered doses, and the like can be readily made a qualified clinician.

[0347] The first tapered dose may be administered at any time after the previous dose of ibogaine. The first tapered dose can be given once, for example, followed by subsequent further tapered doses, or it can be given multiple times with or without subsequent, further tapered doses (e.g., second, third, fourth, etc. tapered doses), which likewise can be given once or over multiple administrations, for example. In some embodiments, the first tapered dose is given after the first dose of ibogaine. In some embodiments, the first tapered dose is
given after the second, third, or a subsequent dose of ibogaine. In some embodiments, the first tapered dose is administered one hour, 6 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, or more after the previous dose of ibogaine. Similarly, second, third, fourth, etc. tapered doses, if given, can be given one hour, 6 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, or more after the previous dose of ibogaine.

[0348] In some embodiments, one tapered dose is given to achieve the desired lower therapeutic dose. In some embodiments, two tapered doses are given to achieve the desired lower therapeutic dose. In some embodiments, three tapered doses are given to achieve the desired lower therapeutic dose. In some embodiments, four or more tapered doses are given to achieve the desired lower therapeutic dose. Determination of the tapered doses, number of tapered doses, and the like can be readily made a qualified clinician.

[0349] In some embodiments, the patient undergoes long-term (e.g., one month, three months, six months, one year or longer) treatment with maintenance doses of ibogaine, ibogaine derivative, or salt and/or solvate thereof. In some embodiments, the patient is treated for acute withdrawal with therapeutic doses of ibogaine as described above, and then the amount of ibogaine is reduced to maintenance levels after acute withdrawal symptoms would be expected to have subsided. Acute withdrawal symptoms generally are the most pronounced in the first week after cessation of alcohol use, although acute withdrawal may last as long as six weeks or more.

[0350] In some embodiments, the composition is administered via sublingual, intranasal, or intrapulmonary delivery. In one aspect, the invention provides administering a pharmaceutical composition comprising a pharmaceutically effective amount of ibogaine or ibogaine derivative and a pharmaceutically acceptable excipient, wherein the therapeutically effective amount of ibogaine or ibogaine derivative is an amount that delivers an aggregate amount of ibogaine or ibogaine derivative of about 50 ng to less than 100 µg per kg body weight per day. In some aspects, the therapeutically effective amount of ibogaine or ibogaine derivative is an amount that delivers an aggregate amount of ibogaine or ibogaine derivative of about 50 ng to about 50 µg per kg body weight per day. In some aspects, the therapeutically effective amount of ibogaine or ibogaine derivative is an amount that delivers an aggregate amount of ibogaine or ibogaine derivative of about 50 ng to about 10 µg per kg body weight per day. In some aspects, the therapeutically effective amount of ibogaine or ibogaine derivative is an amount that delivers an aggregate amount of ibogaine or ibogaine derivative...
derivative of about 50 ng to about 1 µg per kg body weight per day. In some aspects, the composition is administered once per day. In some aspects, the composition is administered two or more times per day. In some embodiments, the composition is administered less than once a day, for example once every two days, once every three days, once every four days, once a week, etc.

[0351] In some embodiments, the composition is administered via oral, transdermal, internal, pulmonary, rectal, nasal, vaginal, lingual, intravenous, intraarterial, intramuscular, intraperitoneal, intracutaneous or subcutaneous delivery.

[0352] A particularly suitable composition comprises a composition suitable for a transdermal route of delivery in which the ibogaine or ibogaine derivative is applied as part of a cream, gel or, preferably, patch (for examples of transdermal formulations, see U.S. Pat. Nos. 4,806,341; 5,149,538; and 4,626,539, each of which are incorporated herein by reference).

[0353] In one embodiment, the QT interval is not prolonged more than about 50 ms. In one embodiment, the QT interval is not prolonged more than about 40 ms. In one embodiment, the QT interval is not prolonged more than about 30 ms. In one embodiment, the QT interval is not prolonged more than about 20 ms. In one embodiment, the QT interval is not prolonged more than about 10 ms.

Formulations

[0354] This invention further relates to pharmaceutically acceptable formulations comprising a unit dose of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the amount of ibogaine is sufficient to provide an average serum concentration of about 50 ng/mL to about 850 ng/mL when administered to a patient. In other embodiments, the amount of ibogaine is sufficient to provide an average serum concentration of about 50 ng/mL to about 400 ng/mL when administered to a patient.

[0355] In some embodiments, the unit dose of ibogaine is administered in one or more dosings.

[0356] In one embodiment, the amount of ibogaine is sufficient to provide an average serum concentration of ibogaine from about 50 ng/mL to about 800 ng/mL or about 60 ng/mL to about 800 ng/mL. In one embodiment, the amount of ibogaine is sufficient to
provide an average serum concentration of ibogaine from about 50 ng/mL to about 700 ng/mL or about 60 ng/mL to about 700 ng/mL. In one embodiment, the amount of ibogaine is sufficient to provide an average serum concentration of ibogaine from about 50 ng/mL to about 600 ng/mL, or about 60 ng/mL to about 600 ng/mL. In a preferred embodiment, the amount of ibogaine is sufficient to provide an average serum concentration of ibogaine from about 50 ng/mL to about 500 ng/mL, or about 60 ng/mL to about 500 ng/mL. In one embodiment, the amount of ibogaine is sufficient to provide an average serum concentration of ibogaine from about 50 ng/mL to about 400 ng/mL, or about 60 ng/mL to about 400 ng/mL. In one embodiment, the amount of ibogaine is sufficient to provide an average serum concentration of ibogaine from about 50 ng/mL to about 300 ng/mL, or about 60 ng/mL to about 300 ng/mL. In one embodiment, the amount of ibogaine is sufficient to provide an average serum concentration of ibogaine from about 50 ng/mL to about 200 ng/mL, or about 60 ng/mL to about 200 ng/mL. In one embodiment, the amount of ibogaine is sufficient to provide an average serum concentration of ibogaine from about 50 ng/mL to about 100 ng/mL, or about 60 ng/mL to about 100 ng/mL. The ranges include both extremes as well as any subranges between.

[0357] In some embodiments, the formulation is designed for periodic administration, such as once, twice, three time, four times or five time daily with ibogaine or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the administration is once daily, or once every second day, once every third day, three times a week, twice a week, or once a week. The dosage and frequency of the administration depends on the route of administration, content of composition, age and body weight of the patient, condition of the patient, without limitation. Determination of dosage and frequency suitable for the present technology can be readily made a qualified clinician.

Delivery method

[0358] The compositions, provided herein or known, suitable for administration in accordance with the methods provided herein, can be suitable for a variety of delivery modes including, without limitation, sublingual, intrapulmonary, or intranasal delivery. Compositions suitable for internal, pulmonary, rectal, nasal, vaginal, lingual, intravenous, intra-arterial, intramuscular, intra-peritoneal, intra-cutaneous and subcutaneous routes may also be used. Other dosage forms include tablets, capsules, pills, powders, aerosols, suppositories, parenterals, and oral liquids, including suspensions, solutions and emulsions.
Sustained release dosage forms may also be used. All dosage forms may be prepared using methods that are standard in the art (see e.g., Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton Pa. 1980).

The compositions provided herein can also be used in conjunction with any of the vehicles and excipients commonly employed in pharmaceutical preparations, e.g., talc, gum Arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous solvents, oils, paraffin derivatives, glycols, etc. Coloring and flavoring agents may also be added to preparations, particularly to those for oral administration. Solutions can be prepared using water or physiologically compatible organic solvents such as ethanol, 1,2-propylene glycol, polyglycols, dimethylsulfoxide, fatty alcohols, triglycerides, partial esters of glycerine and the like. Parenteral compositions containing ibogaine may be prepared using conventional techniques that may include sterile isotonic saline, water, 1,3-butanediol, ethanol, 1,2-propylene glycol, polyglycols mixed with water, Ringer's solution, etc.

The compositions utilized herein may be formulated for aerosol administration, particularly to the respiratory tract and including intrapulmonary or intranasal administration. The compound will generally have a small particle size, for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient may be provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), (for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane), carbon dioxide or other suitable gases. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively, the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone. In some embodiments, the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form, for example in capsules or cartridges, gelatin or blister packs, from which the powder may be administered by means of an inhaler.

In some embodiments, ibogaine is administered orally, which may conveniently be provided in tablet, caplet, sublingual, liquid or capsule form. In certain embodiments, the ibogaine is provided as ibogaine HC1, with dosages reported as the amount of free base.
ibogaine. In some embodiments, the ibogaine HCl is provided in hard gelatin capsules containing only ibogaine HCl with no excipients.

[0362] The compositions utilized herein may be formulated for sublingual administration, for example as sublingual tablets. Sublingual tablets are designed to dissolve very rapidly. The formulations of these tablets contain, in addition to the drug, a limited number of soluble excipients, usually lactose and powdered sucrose, but sometimes dextrose and mannitol.

[0363] It has been discovered that ibogaine has a bitter taste to at least some patients. Accordingly, compositions for oral use (including sublingual, inhaled, and other oral formulations) may be formulated to utilize taste-masking technologies. A number of ways to mask the taste of bitter drugs are known in the art, including addition of sugars, flavors, sweeteners, or coatings; use of lipoproteins, vesicles, and/or liposomes; granulation; microencapsulation; numbing of taste buds; multiple emulsion; modification of viscosity; or salt formation; inclusion or molecular complexes; ion exchange resins; and solid dispersion. Any method of masking the bitterness of the compound of the invention may be used.

**Patient Pre-screening and Monitoring**

[0364] Pre-screening of patients before treatment with ibogaine and/or monitoring of patients during ibogaine treatment may be required to ensure that QT interval is not prolonged beyond a certain value. For example, QT interval greater than 500 ms can be considered dangerous for individual patients. Pre-screening and/or monitoring may be necessary at high levels of ibogaine treatment.

[0365] In some embodiments, a patient receiving ibogaine is monitored in a clinical setting. Monitoring may be necessary to ensure the QT interval is not prolonged to an unacceptable degree. A "clinical setting" refers to an inpatient setting (e.g., inpatient clinic, hospital, rehabilitation facility) or an outpatient setting with frequent, regular monitoring (e.g., outpatient clinic that is visited daily to receive dose and monitoring). Monitoring includes monitoring of QT interval. Methods for monitoring of QT interval are well-known in the art, for example by ECG.

[0366] In one embodiment, a patient receiving ibogaine is not monitored in a clinical setting. In one embodiment, a patient receiving ibogaine is monitored periodically, for example daily, weekly, monthly, or occasionally.
In one aspect, this invention relates to a method for treating a disease or disorder or symptoms of a disease or disorder, comprising selecting addicted dependent patient who is prescreened to evaluate the patient’s expected tolerance for prolongation of QT interval, administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 850 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse or symptoms while maintaining a QT interval of less than 500 ms during said treatment. In some embodiments, the concentration is sufficient to attenuate said abuse or symptoms while maintaining a QT interval of less than about 470 ms during treatment. Preferably, the concentration is sufficient to attenuate said abuse or symptoms while maintaining a QT interval of less than about 450 ms during treatment. In one embodiment, the concentration is sufficient to attenuate said abuse or symptoms while maintaining a QT interval of less than about 420 ms during treatment.

In one embodiment, prescreening of the patient comprises ascertaining that ibogaine treatment will not result in a QT interval over about 500 ms. In one embodiment, prescreening of the patient comprises ascertaining that ibogaine treatment will not result in a QT interval over about 470 ms. In one embodiment, prescreening comprises ascertaining that ibogaine treatment will not result in a QT interval over about 450 ms. In one embodiment, prescreening comprises ascertaining that ibogaine treatment will not result in a QT interval over about 420 ms. In one embodiment, prescreening comprises determining the patient's pre-treatment QT interval.

As it relates to pre-screening or pre-selection of patients, patients may be selected based on any criteria as determined by the skilled clinician. Such criteria may include, by way of non-limiting example, pre-treatment QT interval, pre-existing cardiac conditions, risk of cardiac conditions, age, sex, general health, and the like. The following are examples of selection criteria for disallowing ibogaine treatment or restricting dose of ibogaine administered to the patient: high QT interval before treatment (e.g., such that there is a risk of the patient’s QT interval exceeding 500 ms during treatment); congenital long QT syndrome; bradycardia; hypokalemia or hypomagnesemia; recent acute myocardial infarction; uncompensated heart failure; and taking other drugs that increase QT interval. In some embodiments, the methods can include selecting and/or administering/providing ibogaine to a patient that lacks one more of such criteria.
In one embodiment, this invention relates to pre-screening a patient to determine if the patient is at risk for prolongation of the QT interval beyond a safe level. In one embodiment, a patient at risk for prolongation of the QT interval beyond a safe level is not administered ibogaine. In one embodiment, a patient at risk for prolongation of the QT interval beyond a safe level is administered ibogaine at a limited dosage.

In some embodiments, the kit of parts includes a dosing treatment schedule that provides an attending clinician the

Kit of Parts

One aspect of this invention is directed to a kit of parts for the treatment of a disease or disorder and/or symptoms of a disease or disorder as described herein in a patient, wherein the kit comprises a composition comprising ibogaine, ibogaine derivative, or salt and/or solvate thereof and a means for administering the composition to a patient in need thereof. The means for administration to a patient can include, for example, any one or combination of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof, a transdermal patch, a syringe, a needle, an IV bag comprising the composition, a vial comprising the composition, an inhaler comprising the composition, etc. In one embodiment, the kit of parts further comprises instructions for dosing and/or administration of the composition.

In some aspects, the invention is directed to a kit of parts for administration of ibogaine, the kit comprising multiple delivery vehicles, wherein each delivery vehicle contains a discrete amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof, and further wherein each delivery vehicle is identified by the amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof provided therein; and optionally further comprising a dosing treatment schedule in a readable medium. In some embodiments, the dosing treatment schedule includes the amount of ibogaine required to achieve each average serum level is provided. In some embodiments, the kit of parts includes a dosing treatment schedule that provides an attending clinician the
ability to select a dosing regimen of ibogaine based on the sex of the patient, mass of the
patient, and the serum level that the clinician desires to achieve. In some embodiments, the
dosing treatment schedule further provides information corresponding to the volume of blood
in a patient based upon weight (or mass) and sex of the patient. In an embodiment, the
storage medium can include an accompanying pamphlet or similar written information that
accompanies the unit dose form in the kit. In an embodiment, the storage medium can include
electronic, optical, or other data storage, such as a non-volatile memory, for example, to store
a digitally-encoded machine-readable representation of such information.

[0374] The term "delivery vehicle" as used herein refers to any formulation that can be
used for administration of ibogaine to a patient. Non-limiting, exemplary delivery vehicles
include caplets, pills, capsules, tablets, powder, liquid, or any other form by which the drug
can be administered. Delivery vehicles may be intended for administration by oral, inhaled,
injected, or any other means.

[0375] The term "readable medium" as used herein refers to a representation of data that
can be read, for example, by a human or by a machine. Non-limiting examples of human-
readable formats include pamphlets, inserts, or other written forms. Non-limiting examples of
machine-readable formats include any mechanism that provides (i.e., stores and/or transmits)
information in a form readable by a machine (e.g., a computer, tablet, and/or smartphone).
For example, a machine-readable medium includes read-only memory (ROM); random
access memory (RAM); magnetic disk storage media; optical storage media; and flash
memory devices. In one embodiment, the machine-readable medium is a CD-ROM. In one
embodiment, the machine-readable medium is a USB drive. In one embodiment, the
machine-readable medium is a Quick Response Code (QR Code) or other matrix barcode.

[0376] In some aspects, the machine-readable medium comprises software that contains
information regarding dosing schedules for the unit dose form of ibogaine and optionally
other drug information. In some embodiments, the software may be interactive, such that the
attending clinician or other medical professional can enter patient information. In a non-
limiting example, the medical professional may enter the weight and sex of the patient to be
treated, and the software program provides a recommended dosing regimen based on the
information entered. The amount and timing of ibogaine recommended to be delivered will
be within the dosages that result in the serum concentrations as provided herein.
In some embodiments, the kit of parts comprises multiple delivery vehicles in a variety of dosing options. For example, the kit of parts may comprise pills or tablets in multiple dosages, such as 240 mg, 120 mg, 90 mg, 60 mg, 30 mg, 20 mg, and/or 10 mg of ibogaine per pill. Each pill is labeled such that the medical professional and/or patient can easily distinguish different dosages. Labeling may be based on printing or embossing on the pill, shape of the pill, color of pill, the location of the pill in a separate, labeled compartment within the kit, and/or any other distinguishing features of the pill. In some embodiments, all of the delivery vehicles within a kit are intended for one patient. In some embodiments, the delivery vehicles within a kit are intended for multiple patients.

One aspect of this invention is directed to a kit of parts for the treatment of a disease or disorder described herein, wherein the kit comprises a unit dose form of ibogaine, ibogaine derivative, or salt and/or solvate thereof. The unit dose form provides a patient with an average serum level of ibogaine of from about 50 ng/mL to about 800 ng/mL or about 60 ng/mL to about 800 ng/mL. In one embodiment, the unit dose form provides a patient with an average serum level of ibogaine of from about 50 ng/mL to about 400 ng/mL or about 60 ng/mL to about 400 ng/mL.

In some embodiments, the unit dose form comprises one or multiple dosages to be administered periodically, such as once, twice, three time, four times or five time daily with ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the administration is once daily, or once every second day, once every third day, three times a week, twice a week, or once a week. The dosage and frequency of the administration depends on criteria including the route of administration, content of composition, age and body weight of the patient, condition of the patient, sex of the patient, without limitation, as well as by the severity of the addiction. Determination of the unit dose form providing a dosage and frequency suitable for a given patient can readily be made by a qualified clinician.

These dose ranges may be achieved by transdermal, oral, or parenteral administration of ibogaine or a pharmaceutically acceptable salt and/or solvate thereof in unit dose form. Such unit dose form may conveniently be provided in transdermal patch, tablet, caplet, liquid or capsule form. In certain embodiments, the ibogaine is provided as ibogaine HC1, with dosages reported as the amount of free base ibogaine. In some embodiments, the ibogaine HC1 is provided in hard gelatin capsules containing only ibogaine HC1 with no

103
excipients. In some embodiments, ibogaine is provided in saline for intravenous administration.

[0381] In another aspect, provided herein is a kit of parts for administration of ibogaine, the kit comprising multiple delivery vehicles, wherein each delivery vehicle contains a discrete amount of ibogaine and further wherein each delivery vehicle is identified by the amount of ibogaine provided therein; and optionally further comprising a dosing treatment schedule in a readable medium.

[0382] In one embodiment, the amount of ibogaine required to achieve each maximum serum level is provided in the readable medium. In another embodiment, the readable medium is a computer-readable medium. In another embodiment, the multiple delivery vehicles contain different amounts of ibogaine. In another embodiment, the dosing treatment schedule provides an attending clinician the ability to select a dosing regimen of ibogaine based on the sex of the patient, mass of the patient, and the serum level that the clinician desires to achieve. In another embodiment, the dosing treatment schedule further provides information corresponding to the volume of blood in a patient based upon weight and sex of the patient.
EXAMPLES

[0383] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

Example 1: Effect Of Low Dose Of Ibogaine On Smoking Cessation

[0384] A female habitual smoker intranasally absorbs a milligram amount of ibogaine hydrochloride. During a period of several hours, any craving to smoke is measured periodically.

Example 2. Efficacy Of Ibogaine, Ibogaine Derivative, Or A Pharmaceutically Acceptable Salt Thereof In Humans

[0385] The efficacy of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt thereof is evaluated in alcohol-dependent participants in a randomized, placebo-controlled, double-blind trial. Patients are administered placebo or 60 mg or 120 mg of the compound and QT interval is measured.

Example 3. Efficacy Of Ibogaine In Treating Substance Dependency

[0386] The efficacy of ibogaine is evaluated in substance-dependent participants in a randomized, placebo-controlled, double-blind trial. Patients are administered 60 mg or 120 mg of the compound and QT interval is measured.

Example 4. Use Of Ibogaine To Treat Chronic Pain In Humans

[0387] Six patients experiencing chronic pain are screened and selected to receive administration of ibogaine. Four patients intranasally absorb a milligram amount of ibogaine hydrochloride and the remaining two patients receive a placebo. The level of pain and pain relief of the patients are measured.

Example 5. Forced Swim Test (FST) With Rats

[0388] Animals: Male Sprague-Dawley rats (Taconic Farms, N.Y.) are used in all experiments. Rats are housed 5 per cage and maintained on a 12:12-h light-dark cycle. Rats are handled for 1 minute each day for 4 days prior to behavioral testing.

[0389] Drug Administration: Animals are randomly assigned to receive a single intraperitoneal administration of vehicle (2.5% EtOH/2.5% Tween-80), imipramine (positive
control; 60 mg/kg), or Test Compound 60 minutes before the start of the 5 minute test period. All injections are given using 1 cc tuberculin syringe with 26 3/8 gauge needles (Becton-Dickinson, VWR Scientific, Bridgeport, N.J.). The volume of injection is 1 ml/kg.

**Experimental Design:** The procedure used in this study employs a water depth of 31 cm. The greater depth in this test prevents the rats from supporting themselves by touching the bottom of the cylinder with their feet. Swim sessions are conducted by placing rats in individual plexiglass cylinders (46 cm tall and 20 cm diameter) containing 23-25°C water. Swim tests are conducted always between 9:00 and 17:00 hours and included an initial 15-minute conditioning test followed 24 hours later by a 5-minute test. Drug treatments are administered 60 minutes before the 5-minute test period. Following all swim sessions, rats are removed from the cylinders, dried with paper towels and placed in a heated cage for 15 minutes and returned to their home cages. All test sessions are videotaped using a color video camera and recorded for scoring later.

**Behavioral Scoring:** The rat's behavior is rated at 5 second intervals during the 5 minute test by a single individual, who is blind to the treatment condition. Scored behaviors are: 1. Immobility—rat remains floating in the water without struggling and is only making those movements necessary to keep its head above water; 2. Climbing—rat is making active movements with its forepaws in and out of the water, usually directed against the walls; 3. Swimming—rat is making active swimming motions, more than necessary to merely maintain its head above water, e.g. moving around in the cylinder; and 4. Diving—entire body of the rat is submerged.

**Data Analysis:** The forced swim test data (immobility, swimming, climbing, diving) are subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Newman-Keuls test. The data are analyzed using the GraphPad Prism (v2.01) (GraphPad Software, Inc., San Diego, Calif).

**Example 6. Forced Swim Test (FST) With Mice**

**Animals:** DBA/2 mice (Taconic Farms, N.Y.) are used in all experiments. Animals are housed 5 per cage in a controlled environment under a 12:12 hour lightdark cycle. Animals are handled 1 min each day for 4 days prior to the experiment. This procedure includes a mock gavage with a 1.5 inch feeding tube.
[0394] **Drug Administration:** Animals are randomly assigned to receive a single administration of vehicle (5% EtOH/5% Tween-80), Test Compound, or imipramine (60 mg/kg) by oral gavage 1 hour before the swim test.

[0395] **Experimental Design:** The procedure for the forced swim test in the mouse is similar to that described above for the rat, with the following modifications. The cylinder used for the test is a 1 liter beaker (10.5 cm diameter and 15 cm height) filled to 800 ml (10 cm depth) with 23 25°C, water. Only one 5-minute swim test is conducted for each mouse, between 13:00 and 17:00 hours. Drug treatments are administered 30-60 minutes before the 5-minute test period. Following all swim sessions, mice are removed from the cylinders, dried with paper towels and placed in a heated cage for 15 minutes. All test sessions are videotaped using a Sony color video camera and recorder for scoring later.

[0396] **Behavioral Scoring:** The behavior during minutes 2-5 of the test is played back on a TV monitor and scored by the investigator. The total time spent immobile (animal floating with only minimal movements to remain afloat) and mobile (swimming and movements beyond those required to remain afloat) are recorded.

[0397] **Data Analysis:** The forced swim test data (time exhibiting immobility, mobility; seconds) are subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Newman-Keuls test. The data are analyzed using the GraphPad Prism (v2.01) (GraphPad Software, Inc., San Diego, Calif).

**Example 7. Effect of ibogaine on QT interval in humans**

[0398] The safety of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt and/or solvate thereof is evaluated in patients in a randomized, placebo-controlled, double-blind trial. Patients are administered 60 mg or 120 mg of the compound and QT interval is measured.

**Example 8. Effect of ibogaine on depression in humans**

[0399] A male patient, age 55, suffering from depression unrelated to the use of any illicit substance, is treated with ibogaine hydrochloride at a dose of about 1 mg/kg/day for a period of four weeks. During the treatment period, his depression is determined by the patient's self-reporting of a decrease in symptoms and/or changes in one or more of the following tests: HDRS, Hamilton depressed mood item, and CGI-Severity of Illness.
Example 9. Efficacy of ibogaine to modulate opioid tolerance in humans

A female patient, age 59, undergoing opioid analgesic therapy for chronic back pain, is treated with ibogaine hydrochloride at a dose of about 2 mg/kg concurrently with the opioid. The amount of opioid required to treat her back pain after ibogaine treatment is measured.

Example 10. Social Interaction Test (SIT)

**Animals:** Male albino Sprague-Dawley rats (Taconic Farms, N.Y.) are housed in pairs under a 12 hr light dark cycle (lights on at 0700 hrs.) with free access to food and water.

Rats are allowed to acclimate to the animal care facility for 5 days and are housed singly for 5 days prior to testing. Animals are handled for 5 minutes per day. On the test day, weight matched pairs of rats (±5%), unfamiliar to each other, are given identical treatments and returned to their home cages. Animals are randomly divided into 5 treatment groups, with 5 pairs per group, and are given one of the following i.p. treatments: Test Compound (1, 2 or 4 mg/kg), vehicle (1 ml/kg) or chlordiazepoxide (5 mg/kg). Dosing is done 1 hour prior to testing. Rats are subsequently placed in a white perspex test box or arena (54x37x26 cm), whose floor is divided up into 24 equal squares, for 15 minutes. An air conditioner is used to generate background noise and to keep the room at approximately 74°F. All sessions are videotaped using a JVC camcorder (model GR-SZ1, Elmwood Park, N.J.) with either TDK (HG ultimate brand) or Sony 30 minute videocassettes. All sessions are conducted between 13:00 and 16:30 hours. Active social interaction, defined as grooming, sniffing, biting, boxing, wrestling, following and crawling over or under, is scored using a stopwatch (Sportsline model no. 226, 1/100 sec. discriminability). The number of episodes of rearing (animal completely raises up its body on its hind limbs), grooming (licking, biting, scratching of body), and face ishing (i.e. hands are moved repeatedly over face), and number of squares crossed are scored. Passive social interaction (animals are lying beside or on top of each other) is not scored. All behaviors are assessed later by an observer who is blind as to the treatment of each pair. At the end of each test, the box is thoroughly wiped with moistened paper towels.

**Data Analysis:** The social interaction data (time interacting, rearing and squares crossed) are subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Student-Newman-Keuls test. The data are subjected to a test of normality (Shapiro-Wilk
test). The data are analyzed using the GBSTAT program, version 6.5 (Dynamics Microsystems, Inc., Silver Spring, Md., 1997).

Example 11. Efficacy of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt thereof on anxiety-related disorders in humans

[0404] The efficacy of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt thereof is evaluated in participants undergoing treatment for an anxiety-related disorder in a randomized, placebo-controlled, double-blind trial. Patients are not taking any other medications to treat anxiety. Patients are administered placebo or 60 mg or 120 mg of the compound and QT interval is measured.

Example 12. Efficacy of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt thereof on impulse control disorders in humans

[0405] The efficacy of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt thereof is evaluated in participants undergoing treatment for an impulse control disorder in a randomized, placebo-controlled, double-blind trial. Patients are not taking any other medications to treat anxiety. Patients are administered placebo or 60 mg or 120 mg of the compound and QT interval is measured.

Example 13. Efficacy of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt thereof on violence-related disorders in humans

[0406] The efficacy of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt thereof is evaluated in participants undergoing treatment for a violence-related disorder in a randomized, placebo-controlled, double-blind trial. Patients are not taking any other medications to treat anxiety. Patients are administered placebo or 60 mg or 120 mg of the compound and QT interval is measured. Mean prolongation of the QT interval and/or the severity of violent outbursts, are determined by self-evaluation and clinical evaluation.

Example 14. Efficacy of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt thereof on food intake in humans

[0407] The efficacy of ibogaine, ibogaine derivative, or a pharmaceutically acceptable salt thereof is evaluated in participants undergoing treatment for obesity related to over-eating in a randomized, placebo-controlled, double-blind trial. Patients are not taking any other
medications to treat anxiety. Patients are administered placebo or 60 mg or 120 mg of the compound and QT interval is measured. Mean prolongation of the QT interval, weight loss and food intake and/or cravings, are determined by self-evaluation and clinical evaluation.
What is claimed is:

1. A method for treating nicotine addiction 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, wherein said therapeutically effective amount is from about 50 ng to less than 10 µg per kg body weight per day.

2. The method of claim 1, wherein the therapeutically effective amount is from about 50 ng to about 1 µg per kg body weight per day.

3. A method for treating alcohol dependence in a human patient suffering therefrom, comprising administering to the patient a dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to ameliorate said dependence while maintaining a QT interval of less than about 500 ms during said treatment.

4. The method of claim 3, wherein the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered as a single dose or multiple doses.

5. The method of claim 4, wherein the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 1.3 mg/kg to about 4 mg/kg per day.

6. A method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to alcohol dependence, comprising administering to the patient a dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

7. The method of claim 6, wherein the withdrawal symptoms are due to acute withdrawal.
8. The method of claim 6, wherein the ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is administered as a single dose or multiple doses.

9. The method of claim 6, wherein the aggregate dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is from about 1.3 mg/kg to about 4 mg/kg per day.

10. A method to prevent relapse of alcohol abuse in a patient treated to ameliorate said abuse, said method comprising periodically administering to said patient a maintenance dosage of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof, wherein the patient is no longer physically dependent on alcohol.

11. The method of claim 10, wherein the maintenance dosage is less than about 70% of a therapeutic dose, and further wherein the prolongation of the QT interval is no greater than about 30 ms.

12. A method for treating opioid or opioid-like drug abuse in a human patient addicted thereto, comprising administering to the patient a dosage of ibogaine wherein the dosage provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms during said treatment.

13. The method of claim 12, wherein the QT interval is less than about 450 ms.

14. A method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to opioid or opioid-like drug addiction, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

15. A method to prevent relapse of opioid or opioid-like drug abuse in a patient treated to ameliorate said abuse, said method comprising periodically administering to said patient a maintenance dosage of ibogaine wherein the patient is no longer abusing the opioid or opioid-like drug.
16. A method for treating opioid or opioid-like drug abuse in a patient addicted thereto, comprising selecting an addicted patient who is prescreened to evaluate tolerance for prolongation of QT interval, administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms during said treatment.

17. The method of claim 16, wherein the prescreening step comprises ascertaining that treatment with ibogaine, ibogaine derivative, or pharmaceutically acceptable salt thereof will not result in a QT interval greater than about 500 ms.

18. The method of claim 17, wherein the prescreening step comprises ascertaining that treatment with ibogaine will not result in a QT interval greater than about 470 ms.

19. The method of claim 17, wherein the prescreening step comprises ascertaining that treatment with ibogaine will not result in a QT interval greater than about 450 ms.

20. A method for treating substance abuse in a human patient addicted thereto, comprising administering to the patient a dosage of ibogaine, wherein the dosage provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms during said treatment.

21. A method for attenuating withdrawal symptoms in a human patient susceptible to such symptoms due to substance addiction, comprising administering to the patient a dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration being sufficient to attenuate said symptoms while maintaining a QT interval of less than about 500 ms during said treatment.

22. A method to prevent relapse of substance abuse in a patient treated to ameliorate said abuse, said method comprising periodically administering to said patient a maintenance dosage of ibogaine, wherein the patient is no longer abusing the substance.

23. The method of claim 22, wherein the dosage is less than about 70% of a therapeutic dose of ibogaine, and further wherein the prolongation of the QT interval is no greater than about 30 ms.
24. The method of claim 22, wherein the dosage is less than about 70% of the therapeutic
dose, and further wherein the prolongation of the QT interval is no greater than about 20 ms.

25. A method for treating substance abuse in a patient addicted thereto, comprising
selecting an addicted patient who is prescreened to evaluate tolerance for prolongation of QT
interval, administering to the patient a dosage of ibogaine that provides an average serum
concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to
inhibit or ameliorate said abuse while maintaining a QT interval of less than about 500 ms
during said treatment.

26. The method of any one of claims 20-25, wherein the addictive substance is selected
from the group consisting of benzodiazepines, cannabinoids and synthetic cannabinoids,
stimulants, barbiturates, gamma-hydroxybutyrate (GHB), ketamine, PCP, dexamethorphan
(DXM), lysergic acid diethylamide (LSD), mescaline, anabolic steroids, and derivatives of
each thereof.

27. A method for treating pain in a patient, comprising administering to the patient a
dosage of ibogaine that provides an average serum concentration of about 50 ng/mL to about
500 ng/mL, said concentration being sufficient to alleviate and/or inhibit said pain while
maintaining a QT interval of less than about 500 ms during said treatment.

28. A method for alleviating pain symptoms in a human patient susceptible to such
symptoms, comprising administering to the patient a dosage of ibogaine that provides an
average serum concentration of about 50 ng/mL to about 400 ng/mL, said concentration
being sufficient to alleviate said pain symptoms while maintaining a QT interval of less than
about 500 ms during said treatment.

29. The method of claim 28, wherein the pain symptoms are due to chronic pain.

30. A method for treating depression and/or posttraumatic stress disorder 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,
wherein the patient is not addicted to cocaine or an opiate, and further wherein the
therapeutically effective amount provides an efficacious average ibogaine or ibogaine
derivative serum level of between about 50 ng/mL and about 400 ng/mL while maintaining a
QT interval of less than about 500 ms during said treatment.
31. A method for modulating tolerance to an opioid analgesic in a patient undergoing opioid analgesic therapy, the method comprising interrupting or administering concurrently with said opioid analgesic therapy an amount of ibogaine, ibogaine derivative or pharmaceutically acceptable salt and/or solvate thereof that provides an average serum concentration of about 50 ng/mL to about 500 ng/mL, said concentration being sufficient to re-sensitize the patient to the opioid as an analgesic while maintaining a QT interval of less than about 500 ms during said treatment.

32. A method for treating an anxiety-related disorder 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, wherein the patient is not addicted to cocaine or an opiate, and further wherein the therapeutically effective amount provides an efficacious average ibogaine serum level of between about 50 ng/mL and about 180 ng/mL while maintaining a QT interval of less than about 500 ms during said treatment.

33. The method of claim 32, wherein the anxiety-related disorder is selected from the group consisting of generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, and social anxiety disorder.

34. A method for treating an impulse control disorder 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, wherein the patient is not addicted to cocaine or an opiate, and further wherein the therapeutically effective amount provides an efficacious average ibogaine serum level of between about 50 ng/mL and about 180 ng/mL while maintaining a QT interval of less than about 500 ms during said treatment.

35. The method of claim 34, wherein the impulse control disorder is selected from the group consisting of borderline personality disorder, conduct disorder, antisocial personality disorder, attention deficit hyperactivity disorder, attention deficit disorder, schizophrenia, mood disorders, pathological gambling, pyromania, intermittent explosive disorder, kleptomania, sexual compulsion, paraphilia, internet addiction, trichotillomania, pathological skin picking, and compulsive shopping.

36. A method for regulating food intake and/or attenuating food craving 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, wherein the patient is not addicted to cocaine or an opiate, and further wherein the therapeutically effective amount provides an efficacious average ibogaine serum level of between about 50 ng/mL and about 180 ng/mL while maintaining a QT interval of less than about 500 ms during said treatment.

37. A method for treating an anger-related disorder 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, and further wherein the therapeutically effective amount provides an efficacious average ibogaine serum level of between about 50 ng/mL and about 180 ng/mL while maintaining a QT interval of less than about 500 ms during said treatment.

38. A pharmaceutical composition comprising a therapeutically effective amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof and a pharmaceutically acceptable excipient, wherein the therapeutically effective amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt and/or solvate thereof is an amount that delivers an aggregate amount of ibogaine of about 50 ng to less than 10 µg per kg body weight per day.

39. The pharmaceutical composition of claim 6, wherein the therapeutically effective amount of ibogaine, ibogaine derivative, or pharmaceutically acceptable salt thereof is an amount that delivers an aggregate amount of ibogaine of about 50 ng to about 1 µg per kg body weight per day.

40. A pharmaceutically acceptable formulation comprising a unit dose of ibogaine wherein the amount of ibogaine is sufficient to provide a serum concentration of about 50 ng/mL to about 500 ng/mL when administered to a patient.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K 31/404(2006.01)i, A61K 31/55(2006.01)i, A61K 31/4738(2006.01)i, A61P 25/30(2006.01)i, A61P 25/34(2006.01)i

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 31/404; A61K 31/55; A61K 31/135; A61K 31/445; A61K 31/4738; A61P 25/30; A61P 25/34

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: ibogaine, alcohol dependence, nicotine addiction

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 4857523 A (LOJST0F, H. S.) 15 August 1989 See abstract ; examples 1-5 ; and claims 1-9</td>
<td>38-40</td>
</tr>
<tr>
<td>X</td>
<td>WO 2008-039179 A (ADDICTION RESEARCH INSTITUTE, INC.) 03 April 2008 See claims 1-6</td>
<td>38-40</td>
</tr>
<tr>
<td>X</td>
<td>US 5925634 A (OLNEY, J. W.) 20 July 1999 See abstract ; columns 14-16 ; and claim 3</td>
<td>38-40</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

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
20 May 2015 (20.05.2015)

Date of mailing of the international search report
20 May 2015 (20.05.2015)

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongna-ro, Seo-gu, Daejeon Metropolitan City, 302-701,
Republic of Korea
Facsimile No. +82 42 472 7140

Authorized officer
LEE, Jeong A
Telephone No. +82-42-481-8740

Form PCT/ISA/210 (second sheet) (January 2015)
**INTERNATIONAL SEARCH REPORT**

**International application No.**
PCT/US2015/018356

### Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: 1-37  
   Because they relate to subject matter not required to be searched by this Authority, namely:  
   Claims 1-37 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.

2. **□** Claims Nos.:  
   Because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **□** Claims Nos.:  
   Because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **□** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **□** As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. **□** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **□** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **□** The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- **□** The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- **□** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 4857523 A</td>
<td>15/08/1989</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>WO 2008-039179 Al</td>
<td>03/04/2008</td>
<td>CA 2664935 A</td>
<td>03/04/2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2083825 A</td>
<td>05/08/2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 197804 DO</td>
<td>24/12/2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>us 5474990 A</td>
<td>12/12/1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>us 5616580 A</td>
<td>01/04/1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>us 5629307 A</td>
<td>13/05/1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>us 5767130 A</td>
<td>16/06/1998</td>
</tr>
</tbody>
</table>