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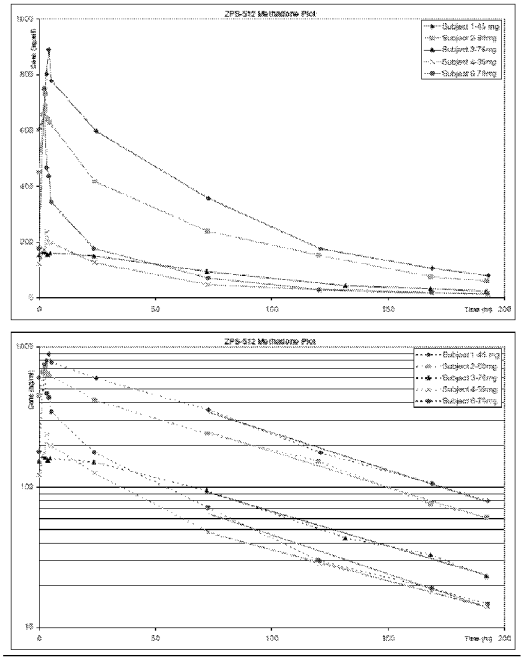
(54) Title: METHOD FOR NORIBOGAINE TREATMENT OF ADDICTION IN PATIENTS ON METHADONE

Figure 1



(57) Abstract: A short treatment with noribogaine shows promise for treating drug dependency. Many opioid addicts are treated with methadone. We have found that giving noribogaine to mammal concurrently being administered methadone surprisingly exacerbates methadone's negative side-effects, and increases the risk of death. Therefore, prior to noribogaine treatment, a patient on methadone therapy undergoes a period of methadone abstinence to wash out the methadone. Surprisingly, noribogaine does not react negatively to morphine. Therefore, the methadone regimen is replaced with morphine prior to noribogaine treatment.

WO 2014/143201 A1

METHOD FOR NORIBOGAINE TREATMENT OF ADDICTION IN PATIENTS ON METHADONE

Field of the Invention

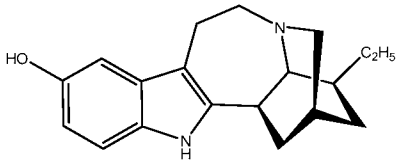
[0001] This invention relates to the administration of noribogaine for the treatment of addiction, and avoiding negative drug interactions. The invention is particularly relevant in the treatment of opioid addiction in human patients who are currently treated with methadone.

State of the Art

[0002] Current treatments for opiate drug dependency include replacing the addictive opiate with another, less-harmful drug that, in theory, is slowly tapered. Methadone, a synthetic opioid, is often used as an opioid replacement for the treatment of heroin addiction, in part because it is slowly metabolized and does not give a "high" associated with opioids. While methadone is effective for reducing illicit drug use in dependent individuals, methadone administration must be maintained indefinitely in these individuals to prevent relapse. In fact, studies have reported over 80% relapse in individuals that discontinued methadone maintenance treatment. Methadone is also addictive, in both patients who were previously addicted to opioids and for the millions who are prescribed methadone for the treatment of pain. Such addiction is often manifested by the desire of patients to increase the amount of methadone used over time.

[0003] The side effects of methadone include heart arrhythmia, and the risk of overdose when combined with other tranquilizers or when dosed too frequently, especially in view of the long-half-life of methadone, *in vivo*. Methadone is now associated with more deaths than any other prescription painkiller, according to the CDC. There is a therefore a need for a treatment that rids the patient of drug dependency including opioid and methadone dependency.

[0004] Noribogaine, also known as 12-hydroxyibogaine or 12-O-demethylibogaine, is a dominant metabolite of ibogaine. Noribogaine can be depicted by the following formula:



[0005] Noribogaine and its pharmaceutically acceptable salts have recently received significant

attention as a non-addictive alkaloid for the treatment of drug dependency (U.S. Patent No. 6,348,456).

SUMMARY OF THE INVENTION

[0006] This invention is based on the discovery that noribogaine negatively interacts with methadone, such administration of noribogaine to mammal concurrently being administered methadone at high doses surprisingly exacerbates methadone's negative side-effects, including the risk of death. Based on this discovered interaction between methadone and noribogaine, it is important that (a) methadone is not administered during or shortly after noribogaine administration; (b) methadone therapy is discontinued prior to noribogaine administration and/or (c) patients are screened for methadone levels prior to administration of noribogaine. The interaction between methadone and noribogaine is relevant to several different classes of patients.

[0007] In one aspect of the invention, the patient is on methadone therapy. As the amount of methadone in the plasma of a methadone treated patient is dependent on that patient's methadone intake, rate of metabolism and other factors, the direct administration of noribogaine to a methadone treated patient is contra-indicated. Therefore, based on this discovered interaction between methadone and noribogaine, prior to initiation of noribogaine treatment, a patient on methadone therapy undergoes a period of methadone abstinence to wash out all or substantially all of the methadone.

[0008] Accordingly, in a related aspect of the invention, there is provided a method for pretreating an opioid addicted patient undergoing methadone therapy such that the patient qualifies for noribogaine therapy to treat the underlying opioid addiction which method comprises maintaining the patient on a methadone abstinence regimen until sufficient methadone has been removed from the patient's serum thereby allowing said patient to undergo noribogaine therapy.

[0009] In another related aspect of the invention, there is provided a method for treating addiction in an opioid addicted patient undergoing methadone therapy which method comprises confirming that a sufficient amount of methadone has been removed from the patient's serum and then administering a therapeutic amount of noribogaine, a noribogaine derivative or a

pharmaceutically acceptable salt thereof to said patient under conditions wherein the patient is no longer opioid addiction.

[0010] In still another aspect the invention is a method for addiction cessation in a human patient whose addiction is treated with methadone, the method comprising: (a) initiating and maintaining methadone abstinence in the patient for a period of time sufficient to remove all or substantially all of the methadone from the patient's serum; and (b) administration of noribogaine, a noribogaine derivative or a pharmaceutically acceptable salt thereof to said patient under conditions wherein the patient is no longer addicted. The level of methadone or methadone metabolites may be monitored in the mammal, such in a body fluid. The period of time sufficient to remove methadone from the body(i.e. until the level of methadone is reduced to an acceptable risk tolerance level) may be adjusted according to the mammal, their physiologic state, metabolic rate, and the like. In one embodiment, the time sufficient to remove methadone from the body is a period of at least one day, typically several days, a week, or more. In another embodiment, the amount of methadone removed from the body is evaluated by blood tests and preferably all or substantially all of the methadone is removed prior to initiation of noribogaine therapy

[0011] Surprisingly, noribogaine can be administered relatively safely to a patient who has been administered (or to whom will be administerd) morphine. The basis of this greater safety of noribogaine with morphine is unknown. Morphine and other opioids having short serum half-lives in the patient are removed from the patient after administration is terminated, so that noribogaine can be administered Therefore, the methadone regimen may be replaced with morphine or such other opioids prior to noribogaine treatment. However, as morphine satisfies the patient's addiction while exhibiting acceptable short term side effects, cessation of methadone is preferably conducted with the concurrent administration of morphine as the short serum half-life opioid. An extended release morphine may be administered, for example. In a further aspect, the cessation of methadone administration occurs through a gradual reduction in the dose or frequency of administration of methadone. The gradual reduction in the dose or frequency of administration of methadone may be matched with gradual increase in the dose or frequency of administration of a non-methadone opioid.

[0012] In addition to those patients in methadone clinics, the risk of negative interactions

between noribogaine and methadone is especially acute in the population of drug users (i.e., not in methadone clinics), who may fail to report prior administration of methadone or may have unwittingly taken methadone as a contaminant in other drugs. Accordingly, in another aspect of the invention, the patient is not on methadone therapy. In this aspect, the patient may, or may not be addicted to opioids. Such a patient may have been administered methadone either as prescribed for the treatment of pain, or as a behavior associated with addiction. For example, drug addicts may take a variety of drugs and drug cocktails, of indeterminate quality and purity. Accordingly, a patient may have been administered methadone without being on methadone therapy.

[0013] Therefore, in the treatment of addiction in a human patient, the clinician must evaluate the methadone exposure and/or the presence of methadone in the body so as to assess whether and when to initiate noribogaine therapy. Methadone exposure may be assessed through questionnaires and/or assays for the presence of methadone or methadone metabolites in a body fluid. The prevention of methadone exposure may also be facilitated by placing the patient in hospital or other controlled environment.

[0014] The negative drug interactions between noribogaine and methadone may also occur with other drugs. In some embodiments, the exposure to, and presence of, such other drugs is determined prior to administration of noribogaine.

[0015] In another aspect, the patient has been administered noribogaine, and the invention concerns the treatment of the patient after administration of noribogaine. Negative drug interactions may also occur in patients who have been administered noribogaine, and are subsequently administered methadone or another drug that adversely interacts with noribogaine. Accordingly, in a preferred embodiment, the patient is maintained in a clinical/controlled setting until the patient is addiction free and the presence of noribogaine in the patient is removed or substantially removed. Alternatively, the patient may be administered morphine in place of other drugs. However, it is important to note that while the initial treatment of noribogaine can treat physiological addiction, behavioral addiction may cause relapse in the treated patient.

[0016] In further aspects, the patient may require multiple rounds of administration of noribogaine. In this aspect, a method of reducing the likelihood and severity of negative

interactions between noribogaine and a second drug includes the determining the level of such second drug, or its metabolite, and/or controlling access to the second other drug. When the other drug is methadone, the method includes determining the level of methadone or a methadone metabolite in the patient prior to administration of noribogaine. In one embodiment, the level of methadone or a methadone metabolite is determined through examination of a sample from the patient. In another embodiment, the patient is administered a series of questions to determine the likelihood of methadone administration. In another embodiment, the patient is placed in a controlled environment to prevent access to methadone.

[0017] In further aspects, the invention includes kits and compositions for the treatment of addiction, and which contain suitable reagents for the treatment of addiction, detecting the presence of methadone and/or noribogaine.

[0018] The invention also includes methods of counselling a patient of the risk of negative interactions between methadone and noribogaine. In related embodiments, the invention includes materials to educate counselors and patients.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figures 1A-B show the serum concentration (ng/ml) of methadone in healthy patients after administration of a single dose of methadone, in amounts ranging from 39 to 80 mg. Figure 1A is normally scaled, and Figure 1B is the same data on a logarithmic scale.

DETAILED DESCRIPTION

[0020] 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 the present invention will be limited only by the appended claims.

[0021] 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.

1. Definitions

[0022] 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.

[0023] The term "about" when used before a numerical designation, *e.g.*, temperature, time, amount, and concentration, including a range, indicates approximations which may vary by 10 % from the stated value.

[0024] The term "mammal" refers to any mammalian species including without limitation mice, rats, rabbits, dogs, primates and, in particular, humans.

[0025] "Addictive" refers to a compound that, when administered to a mammal can create a dependence of the mammal on the compound. A therapeutic effect amount of an addictive compound on a mammal may decrease with prolonged administration of the addictive compound. When administered to a mammal, an addictive compound may also create a craving in the mammal for more of it. Morphine, heroine, methadone, fentanyl, and the like are addictive compounds: specifically, addictive opioids. Other "addictive drugs" include, without limitation:

(A) Stimulants (psychological addiction, moderate to severe; withdrawal is purely psychological and psychosomatic): Amphetamine, methamphetamine, Cocaine, Caffeine, Nicotine

(B) Sedatives and hypnotics (psychical addiction, mild to severe, and physiological addiction, severe; abrupt withdrawal may be fatal): Alcohol, Barbiturates, glutethimide; Benzodiazepines, particularly alprazolam, flunitrazepam, triazolam, temazepam, and nimetazepam; Z-drugs like zopiclone (which have a similar effect in the body to benzodiazepines); Methaqualone and the related quinazolinone sedative-hypnotics

(C) Opiate and opioid analgesics (psychical addiction, mild to severe, physiological addiction, mild to severe; abrupt withdrawal is unlikely to be fatal): Morphine and codeine, the two naturally occurring opiate analgesics; Semi-synthetic opiates, such as

heroin (diacetylmorphine; morphine diacetate), oxycodone, buprenorphine, and hydromorphone; Fully synthetic opioids, such as fentanyl, meperidine/pethidine, and methadone

[0026] In preferred embodiments, the addictive drugs to be treated are opiates, opioids, cocaine, and/or alcohol. In contrast, noribogaine is not an addictive compound or "addictive drug"

[0027] Likewise, "treating addiction" in a mammal refers to a course of action that decrease the physiological dependence or craving for the addictive substance. The addiction can be to methadone, other opioids, or any other addictive compound.

[0028] "Treating addiction in a mammal being administered methadone" refers to the fact that the mammal is, or is suspected of being, administered methadone. This relates to the risk of a negative interaction between methadone and noribogaine. It is not to be taken as limiting the scope of mammals to those who are addicted to methadone, or other opioids. For example, a mammal may be addicted to nicotine, alcohol or another compound, and is administered methadone for treatment of the addiction. It may also be that methadone is administered to the mammal for provision of analgesia (treatment of pain).

[0029] "Administration" refers to introducing an agent 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, intraarterial, inhalation, vaginal, rectal, nasal, introduction into the cerebrospinal fluid, or instillation into body compartments can be used. In a preferred embodiment, administration is oral. 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.

[0030] For administration of noribogaine, the amount may be 25, 50, 75, 100, 125, 150, 175,

200, 250, 300, 350, 400, 450, or 500 mg. Preferably, the amount is selected from 30, 60, 120, 240, 360 mg per patient, in a single dose.

[0031] Alternatively, the administration of noribogaine may be determined by serum Cmax and or AUC, in order to obtain a therapeutic dose. Administration of a single dose of 30 mg noribogaine free base under fasting conditions gives a C_{max} of 55.9 ng/ml at 1.75 hours after administration, with a mean AUC/24 of 29.2 ng/ml.

[0032] For a single dose of 60 mg noribogaine free base under fasting conditions, the mean C_{max} of 116 ng/ml was observed between 1.75 hours after administration, while the mean AUC/24 ng/ml of 61 was obtained.

[0033] "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.

[0034] The term "substantial" is used to refer to an amount that produces a significant effect. Therefore "without providing any substantial amount" doesn't exclude a small amount that produces little or no effect in the patient. Similarly, the term "substantial proportion" refers to more than about 50% in some cases. It could also refer to more than about 60%, more than about 70%, more than about 80%, more than about 90%, more than about 95%, or more than about 99%.

[0035] The term "substantially all" as used herein refers to a level of drug, such as methadone or noribogaine that is below a level associated with a significant risk of negative interaction. If the level of the drug removed is substantially all of the drug in the mammal, that animal is "negative" for the presence of that certain drug. If the level of the drug removed is not substantially all of that drug in the mammal, that animal is "positive" for the presence of the

drug.

[0036] " The level associated with a significant risk of negative interaction" will vary according to the patient and, especially, the tolerance for the drug. During addiction, the patient will typically have increased the dose and/or frequency of administration such that the level of drug tolerated by the patient would be seriously harmful, and even fatal, to a patient who has not been previously administered the drug. After treatment for addiction, and a period of abstinence, the level of tolerance typically declines. Accordingly, tolerance may be determined by a physician or other qualified person.

[0037] A level not associated with a significant risk of negative interaction may be safely assumed as $1/10^{th}$ of the IC50 of the drug. In other embodiments, a level not associated with a significant risk of negative interaction may be more than 10% of the IC50, such as 20%, 25%, 30%, 40% and 50% of the IC50.

[0038] For noribogaine, the lowest IC50 is 0.04 μM, A serum level of 0.004uM (4nM) or below is not associated with a significant risk of negative interaction and qualifies as "substantially all" of the drug being absent.

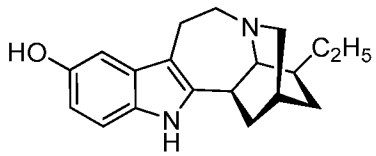
[0039] For methadone, the therapeutic level of methadone ranges from 0.03-0.56 mg/L , according to the US National highway traffic safety administration (www.nhtsa.gov/people/ injury/research/job185drugs/methadone.htm). Accordingly, a patient from whose serum substantially all methadone has been removed has a serum level of methadone ranging from about 1 to about 50% of the initial methadone levels in the blood and, in one preferred embodiment, from about 3μg/L to about 56 μg/L. **[0040]** Figures 1A-B show the serum concentration (ng/ml) of methadone in healthy patients after administration of a single dose of methadone. After 200 hours the serum level of methadone is typically 10% of the Cmax.

[0041] The level of methadone may be determined directly or from metabolites. The primary inactive metabolites of methadone are 2-ethylidene-1.5-dimethyl-3.3diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP), and may be measured in, e.g,. serum and urine. The percentage of a dose excreted in the urine as unchanged methadone and EDDP will vary with the pH of the urine. Urinary excretion of unchanged parent drug is 5-50% and

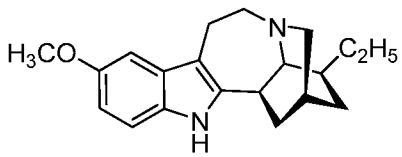
EDDP 3-25%.

[0042] "mu (or μ) opioid receptor" or "mu (or μ) receptor" refers to a class of opioid receptors with higher affinity for enkephalins and beta-endorphins but with lower affinity for dynorphins. mu receptors can mediate acute changes in neuronal excitability via dis-inhibition of presynaptic release of GABA. Mu receptor agonists are compounds that activate the mu receptor and mu receptor antagonists are compounds that prevent activation of the mu receptor.

[0043] The term "higher-affinity mu receptor agonist" refers to a compound having an affinity constant (K value) lower than another compound. For example, noribogaine has been reported to have an affinity constant (K value) of 2.66 for the mu receptor and ibogaine has been reported to have an affinity constant (K value) of 11.04 for the mu receptor (Pearl et al., Brain Research, 675:342-344 (1995)). As such, noribogaine is a higher-affinity mu receptor agonist than ibogaine. **[0044]** "Noribogaine" refers to the compound:



or its pharmaceutically acceptable salt, or solvates of each thereof. Noribogaine binds to the mu receptor that is associated with pain relief and euphoria. With respect to noribogaine's interaction with the mu receptors, it appears that noribogaine acts as a full opioid agonist. In addition, noribogaine elevates brain serotonin levels by blocking synaptic reuptake. Noribogaine is prepared by demethylation of naturally occurring ibogaine:

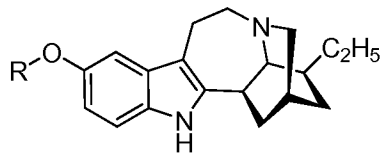


which is isolated from *Tabernanth iboga*, a shrub of West Africa. Demethylation may be accomplished by conventional techniques such as by reaction with boron tribromide/methylene chloride at room temperature followed by conventional purification. See, for example, Huffman, et al., J. Org. Chem. 50:1460 (1985). Methods for the synthesis and purification of noribogaine

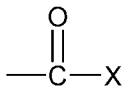
are disclosed in US Patent Application No. 61/333,476, entitled Methods and Compositions for Preparing and Purifying Noribogaine, filed on May 11, 2010, which is hereby incorporated by reference in its entirety.

[0045] "Noribogaine derivatives" refer to those derivatives of noribogaine found in US Patent Nos.8,362,007; published US application Nos. 2013-0165425, 2013-0165414, 2013-0072472, 2013-0165425, 2013-0165414, and 2013-0072472; and Application No. 13/165,626. Each of the above patents and patent applications are incorporated by reference in its entirety.

[0046] Preferably, the present invention provides preferred derivatives of noribogaine such as those having he formula:



wherein R is hydrogen or a hydrolyzable group, such as hydrolysable esters of from about 1 to 12 carbons or a sulfate or phosphate group. Such compounds may be administered either as single compounds, mixtures of compounds or as composition. Generally, in the above formula, R is a hydrogen or a group of the formula:



wherein X is a C_1 -C_{12} group, which is unsubstituted or substituted. For example, X may be a linear alkyl group such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n -decyl, n-undecyl or n-dodecyl, or a branched alkyl group, such as i-propyl or sec-butyl. Also, X may be a phenyl group or benzyl group, either of which may be substituted with lower alkyl groups or lower alkoxy groups. Generally, the lower alkyl and/or alkoxy groups have from 1 to about 6 carbons. For example, the group R may be acetyl, propionyl or benzoyl. However, these groups are only exemplary. Generally, for all groups X, they may either be unsubstituted or substituted with lower alkyl or lower alkoxy groups. For example, substituted X may be o-, m- or p-methyl or methoxy benzyl groups.

[0047] Also encompassed within this invention are derivatives of noribogaine that act as prodrug forms of noribogaine. A prodrug is a pharmacological substance administered in an inactive (or significantly less active) form. Once administered, the prodrug is metabolized in vivo into an active metabolite. In the context of the present claims, "noribogaine derivative" does *not* include ibogaine.

[0048] The present invention is not limited to any particular chemical form of noribogaine and the drug may be given to patients either as a free base 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, 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, and the like. As discussed above, noribogaine itself may be formed from the O-demethylation of ibogaine which, in turn, may be synthesized by methods known in the art (see e.g., Huffman, et al., J. Org. Chem. 50:1460 (1985)).

[0049] "Opiate" refers to a compound extracted from poppy pods and their semi-synthetic counterparts which bind to the opioid receptors.

[0050] "Opioid" refers to a compound that binds to the opioid receptors, including but not limited to mu receptors. Opioids include the opiates and any synthesized drug that attaches itself to the opioid receptors.

[0051] A "synthetic opioid" is a synthetic narcortic that has properties of naturally occurring opiates such as binding to the opioid receptors. Examples of synthetic opioids include methadone, fentanyl, alphamethylfentanyl, alfentanil, sulfentanil, remifentanil, carentanyl, ohmefentanyl, pethidine, ketobemidone, MPPP, allyprodine, prodine, pepap, propoxyphene, dextropropoxphene, dextromoramide, bezitramide, piritramide, methadone, dipipanone, levomethadyl acetate, difenoxin, diphenolylate, loperamide, dezocine, pentazocine, phenazocine, buprenophine, dihydroetorphine, etorphine, butorphanol, nalbuphine, levorphanol, levomethorphan, lefetamine, meptazinol, tilidine, tramadol, tapentadol, nalmefene, naloxone, and naltrexone.

[0052] "Methadone" is an addictive synthetic opioid, used medically as an analgesic, an antitussive and a maintenance anti-addictive for use in patients dependent on opioids.

[0053] "Morphine" is a potent opiate medication. It is the most abundant alkaloid found in opium. It is a powerful analgesic used to relieve severe or agonizing pain. Although morphine has a high potential for addiction, physical addiction may take several months to develop.

[0054] "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.

[0055] "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, hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate 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.

[0056] A "drug exhibiting a negative interaction with noribogaine" can be determined by animal studies and/or clinical trials. The mechanism of the negative interaction between methadone and noribogaine is unknown. Three classes of drugs are ofparticular concern for possible negative interaction with noribogaine. The first class are mu agonists, such as methadone. The second class are are drugs that cause respiratory depression. Drugs that cause respiratory depression include alcohol, benzodiazepines, barbiturates, GHB, and sedatives. Strong opiates, (fentanyl, heroin, morphine, etc.), barbiturates, and the benzodiazepine, temazepam, are particularly notorious for respiratory depression.

[0055] The third class of drugs are those that prolong the QT interval, i.e. the period of time between the Q and T wave in the heart's electrical cycle. Excessive QT elongation is a risk factor for arrhythmia and sudden death. Methadone is well known for prolonging the QT interval of the heart. Other drugs also known for causing QT elongation include clarithromycin (Biaxin), levofloxacin, haloperidol (Haldol), especially when taken concomitantly with a specific cytochrome P450 inhibitor like fluoxetine (Prozac), cimetidine (Tagamet) or grapefruit. Other

examples include amiodarone, lithium, chloroquine, erythromycin, phenothiazines, sotalol, procainamide, quinidine, and cisapride (Propulsid).

[0056] Elongation of the QT interval may also occur with diarrhea, hypomagnesemia and hypokalemia. Hypomagnesemia and hypokalemia is often observed in malnourished individuals and chronic alcoholics. Accordingly, prior to administration of noribogaine, the general health of the patient is assessed, with special attention to serum levels of salts and hydration, particularly Magnesium and Potassium. Dehydratration, hypomagnesemia and/or hypokalemia are treated prior to administration of noribogaine.

[0057] The risk of excessive QT elongation is most pronounced in those with pre-existing QT elongation. Accordingly, in some embodiments, prior to the administration of noribogaine, the patient is examined for QT elongation and arrythmias. According to the best clinical judgment, some patients are contraindictated for noribogaine administration.

[0058] "Therapeutically effective 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 subject 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 an agent, in the context of treating drug dependency, refers to an amount of the agent that attenuates the dependency and/or statistically presents little or no risk of relapse to illicit drug use.

[0059] A "therapeutic level" of noribogaine is an amount of noribogaine that is sufficient to attenuate a drug dependency 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." It is understood that the therapeutic level will depend upon the weight, age, condition and degree of addiction of the patient and that such factors are readily ascertainable by the skilled clinician based on the teachings herein.

[0060] The term "attenuating," "attenuated," or "attenuation" as it applies to drug dependency refers to stabilizing patients and preventing and/or alleviating withdrawal symptoms.

[0061] "The amount of addictive synthetic opioid maintained in the patient" refers to the serum concentration of the addictive synthetic opioid in the patient either once tapering of that opioid is initiated or after cessation of administration of that opioid. "The amount of the noribogaine or the noribogaine derivative administered to or maintained in the patient" refers to a serum concentration of noribogaine or the noribogaine derivative in the patient that is at least as much as the serum concentration that is effective for therapy. The serum concentration of an administered agent may reduce, for example, due to metabolism and/or excretion.

[0062] The term "under the influence" refers to having a measurable serum concentration of an agent.

[0063] "Sub-therapeutic" refers to amounts of noribogaine which when administered either in a single or multiple doses as a single achieve therapeutic serum concentration. A sub-therapeutic serum concentration of noribogaine is typically less than 30 ng/ml (AUC/24), more preferably less than 10 ng/ml (AUC/24).

[0064] "Tapering" refers to the reduction in the amount of, *e.g.*, addictive synthetic opioid agent administered to the patient such that the amount becomes sub-therapeutic and preferably is no longer administered. Tapering occurs over a period of time either in a step wise fashion (*e.g.*, a full dose for 1 hour, 80% of the full dose for 1 hour, 60% of the full dose for 1 hour, *etc.*) or in a continuous manner (*e.g.*, a intravenous drip wherein the amount of the alkaloid analgesic agent is continuously reduced by, for example, computer assisted controls).

[0065] "Treatment", "treating", and "treat" are defined as acting upon a disease, disorder, or condition with an agent 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 disease 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.

[0066] "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, attenuation of dependency, reduced or no dependence on an addictive opioid analgesic agent, and the like.

[0067] "Treating addiction" is defined as a reduction in addictive behavior. This may be determined by a reduction in craving or dependency, such as may be measured in psychological assays or behavioral changes. A behavioral change in addiction may be measured by a reduction in the amount and/or frequency of use of the addictive substance. A period of complete abstinence of use of the addictive drug for at two weeks is strong evidence of treatment. Treatment may also be determined by measuring the level of drugs and metabolites in the patient.

[0068] "Treating addiction" or "treatment of addiction" may also be considered to have at least two separate phases.

[0069] The first phase is treatment of withdrawal from the drug of addiction, herein known as "withdrawal" or "withdrawing". 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 delirium tremens (DTs). Numerous treatments have been developed in attempts to ameliorate such symptoms. For example, a reduction in the dose of the addictive drug, and/or its replacement with a less addictive or less harmful drug ameliorating the symptoms of withdrawal. Administration of noribogaine is effective in reducing in ameliorating the symptoms of withdrawal.

[0070] The second phase is treatment of the behavioral aspects of addiction. Addictive behavior is typically initiated and maintained because, in part, the patient enjoys the experience

of drug administration. Relapse is common. In this phase, success may be measured by a combination of factors, such as (i) reduction in craving (ii) increase in the period of abstinence (iii) reduction of "binge" behavior (iv) reduction in the dose of drug taken (v) reduction in harmful behavior. Repeated treatments may be required. Administration of noribogaine is effective in reducing the behavioral aspects of addiction, although repeat treatments may be required. Such repeat treatments may be (a) as-needed intermittent basis or (b) continuous.

[0071] In preferred embodiments, a discrete administration of noribogaine is effective. That is, noribogaine is administered in one or a few doses over a period of hours. Administration is terminated, until all or substantially all of the noribogaine has been removed from the serum. The dissociative properties of noribogaine are particularly useful in this model of therapy.

[0072] In an alternative embodiment, noribogaine is administered repeatedly to maintain a certain level of noribogaine in the serum, Noribogaine is a mu agonist, and therefore a consistent level of noribogaine is effective in mitigating withdrawal from opioids, and mitigating cravings. Noribogaine is nonaddictive, and is therefore preferable to other "replacement therapy" drugs, such as methadone.

[0073] In the context of long term administration of noribogaine to a patient, the invention includes methods of preventing the administration to the patient of to drugs that negatively interact with noribogaine, such as methadone.

[0074] As used herein, the term "patient" refers to mammals and includes humans and non-human mammals.

Methods of the Invention

[0075] In one embodiment, the noribgaine is administered orally, parenterally, by infusion or transdermally. These routes of administration are discussed in further detail in subsection 3 titled "Routes of Administration."

[0076] In certain embodiments of the present invention, noribogaine is administered to treat the acute addiction phase, in an amount that achieves a serum concentration of about 100 ng/ml to about 9000 ng/ml, measured as Cmax. In another embodiment, noribogaine is administered in

an amount that achieves a serum concentration of about 100 ng/ml to about 1000 ng/ml. In still further embodiments of the invention, the serum concentration achieved is about 300 ng/ml to about 500 ng/ml or about 100 ng/ml to about 500 ng/ml or about 500 ng/ml to about 1000 ng/ml or about 1000 ng/ml to about 1500 ng/ml or about 500 ng/ml to about 1500 ng/ml or about 1000 ng/ml to about 2000 ng/ml or about 1500 ng/ml to about 2000 ng/ml or about 2000 ng/ml to about 3000 ng/ml or about 2000 ng/ml to about 2500 ng/ml or about 2500 ng/ml to about 3000 ng/ml or about 3000 ng/ml to about 4000 ng/ml or about 3000 ng/ml to about 3500 ng/ml or about 3500 ng/ml to about 4000 ng/ml or about 4000 ng/ml to about 5000 ng/ml or about 4000 ng/ml to about 4500 ng/ml or about 4500 ng/ml to about 5000 ng/ml or about 5000 ng/ml to about 6000 ng/ml or about 5000 ng/ml to about 5500 ng/ml or about 5500 ng/ml to about 6000 ng/ml or about 6000 ng/ml to about 7000 ng/ml or about 7000 ng/ml to about 8000 ng/ml or about 8000 ng/ml to about 9000 ng/ml.

[0077] In certain embodiments of the present invention, noribogaine is administered to treat the behavioral addiction phase in an amount that achieves a serum concentration that is substantially less than that for treating the acute addiction stage. Preferably, behavioral addiction can be treated by a dosing of from about 5 to about 50% of the dosing provided in the acute addiction phase and more preferably from about 5 to about 30% of that dosing. In treating behavioral addiction, the dosing of noribogaine can be continuous or intermittent depending on the needs of the patient. In some cases, the patient may be initially treated with a continuous dosing regimen and then switched to an intermittent dosing.

Dosage and Routes of Administration

[0078] The compositions, provided herein or known, 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, intraarterial, intramuscular, intraperitoneal, intracutaneous and subcutaneous routes may also be used. A particularly suitable composition comprises a composition suitable for a transdermal route of delivery in which the noribogaine 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). 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).

[0079] Noribogaine 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 noribogaine 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.

Kit of Parts

[0080] One aspect of the present invention is directed to a kit of parts comprising a composition as disclosed herein 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 a transdermal patch, a syringe, a needle, an IV bag comprising the composition, a vial comprising the composition, etc. For example, a kit can comprise any of the following (a) one or more doses of noribogaine; (b) reagents and/or devices for the administration of noribogaine; (c) one or more doses of morphine; (d) reagents and/or devices for the administration of morphine (e) reagents and/or devices for measuring methadone (f) reagents and/or devices for measuring noribogaine. Such a kit may contain suitable instructions.

EXAMPLES

EXAMPLE 1: Negative interactions between methadone and noribogaine

Overview

[0081] Administration of noribogaine is proposed for the treatment of addiction. Methadone is commonly taken both for pain relief and as part of the treatment of addiction, especially as a replacement for more addictive opiates and opioids such as heroin and oxycodone. Accordingly, the population who are most likely to be administered ibogaine are more likely than average to also be exposed to methadone. The objective of this study was to evaluate the potential adverse effects that may result following oral administration of noribogaine and methadone. Rats were used for evaluating the toxic effects because there is a large historical database of rat toxicology studies and rats have been used in prior toxicology studies with noribogaine. The number of animals selected for this study was considered to be the minimum number required to achieve biological and statistical significance based on 1) the study design and 2) the characteristics of the test article.

[0082] Oral doses for the test article and interaction article were selected as the routes of administration since both drugs are orally bioavailable, oral administration is convenient, in practice for both drugs, and typically preferred by human patients over injection. It is expected that similar results would be obtained with injection.

Materials and methods.

Test System	One hundred and twenty male Sprague Dawley rats were randomly assigned to Groups 1 to 12 (10/group). Animals were received from Charles River Breeding Labs. Animals were approximately 8-10 weeks old and weighed 258-349 g on SD 1 and were identified by ear tags.
Feed	Certified Global Harlan Teklad 2018 Diet (pellets) was provided *ad libitum.* Animals were fasted overnight prior to dosing with both noribogaine and methadone. Food was returned 2 ± 0.5 h following administration of methadone.
Water	Water was provided *ad libitum* via automatic system.
Environment	Animals were individually housed in polycarbonate cages suspended on stainless steel racks. The animals were transferred to stainless steel caging with wire mesh bottoms and a drop pan within three days of dosing. Each cage was affixed with a cage card containing pertinent animal and study information. Animals were housed in a controlled environment. Enrichment (Nyla-Bone) was provided.
Noribogaine	Noribogaine hydrochloride stored in a refrigerator (2-8°C) and protected from light upon receipt. The drug was administered a 35%:65% (v:v) mixture of 0.5% Tween 80 in 5% Dextrose in Water (v:v) and 1.5% (w:v) methylcellulose (400 cps) in Sterile Water for Injection (SWFI), USP, respectively. Stored at ambient temperature (16-26°C).
Methadone	Methadone hydrochloride stored at 16-26°C. For administration, was dissolved in sterile water and stored at ambient temperature..

[0083] Noribogaine in carrier was prepared once. The carrier was prepared by combining an appropriate amount of Tween 80 with 5% Dextrose in Water to prepare a 0.5% v:v solution. The solution was mixed well and stored at 2-8°C. An appropriate amount of methylcellulose was added over approximately 1 minute to boiling SWFI with vigorous mixing, and stored at room temperature to prepare a 1.5% (w:v) suspension, and allowed to cool. It was then formulated to achieve the desired dosage. The correction factor was 1.12 which was based on the hydrochloride salt form of noribogaine. The appropriate amount of noribogaine article was weighed and the carrier solution prepared above was added to provide 35% of the total final volume. The resulting suspension was stirred for at least 30 minutes, the suspension of methylcellulose in water was added to prepare the final total volume, and the suspension was stirred for at least another 30 minutes. The formulation was stored at 2-8°C and protected from light prior to dosing.

[0084] Methadone was mixed in sterile water to the appropriate amount and 2-8°C and protected from light prior to dosing.

Dosing

[0085] Each animal was weighed, and each drug was administered orally at 10 mL/kg of body weight.

Observations

Text Table 3: Animal Observations

Procedure	Frequency of Testing
Cageside Observations	≥ 2 Daily
Physical Examinations	Prior to administration of each test/test article vehicle dose
Postdose (Test Article and Interaction Article) Observations	After test article or its vehicle: Continuously for the first 30 ± 5 min and then at 1 hr ± 10 min intervals until dosing with the interaction article After methadone or its vehicle (which occurred at 4 ± 0.5 hr post administration of the test article or its vehicle): Continuously for the first 60 ± 5 min immediately following methadone or its vehicle, and at 15 ± 5 min intervals for 2 subsequent hours
Body Weights	Prior to administration of each test article/vehicle dose

[0086] On study day 4, all surviving animals were euthanized by carbon dioxide inhalation followed by exsanguination and discarded without necropsy. Animals that were found dead/moribund killed were necropsied as soon as possible after the time of death or discovery and checked for gavage error. No observations were noted and no tissues were collected or preserved; therefore, no discussion of the unscheduled deaths is presented in the results section.

Data Collection and Record Retention

[0087] Electronic data collection, including randomization, dose formulations and dispensing, dosing, animal husbandry, environmental enrichment, clinical, cageside, and postdose observations, and body weights was performed using Provantis™ Version 8 (Instem LSS, Limited; Stone, UK).

RESULTS

Mortality

Text Table 4: Mortality

Treatment Group Number	Noribogaine Dosage (mg/kg)	Methadone Dosage (mg/kg)	Number Dosed	Number Dead after Methadone	% Dead after Methadone	Time to Death after Methadone hh:mm
1	0	0	10	0	0	-
2	0	10	10	0	0	-
3	0	30	10	1	10	1:30
4	0	50	10	3	30	0:55 – 4:17
5	50	0	10	0	0	-
6	50	10	10	0	0	-
7	50	30	10	6	60	1:45 – 4:05
8	50	50	10	9	90	0:40 – 4:01
9	150	0	10	0	0	-
10	150	10	10	6	60	0:25 – 1:15
11	150	30	10	10	100	0:10 – 2:00[a]
12	150	50	10	10	100	0:22 – 0:47

a - Animal 11982 (11m) was found dead on SD 2 at the morning mortality check; hence, the exact time of death is not available and so the range of 0:10 -2:00 is for 9 animals.

[0088] There was no mortality associated with administration of noribogaine at doses of 0, 50, and 150 mg/kg followed by the interaction article vehicle. Mortality occurred in most groups receiving methadone alone or in combination with noribogaine; the exception was Group 2 in which no mortaility occurred following a 10 mg/kg dose of methandone without prior administration of noribogaine. The lowest incidence of mortality occurred in those groups that received methadone alone (Treatment Groups 1 - 4); the mortality rate was 0, 10, and 30% at doses of 10, 30, and 50 mg/kg, respectively. When animals were pretreated with noribogaine the mortality rate increased and occurred at lower methadone doses when compared to the mortality rates following administration of methadone alone. For example in the treatment groups that received 150 mg/kg of noribogaine prior to methadone (Treatment Groups 9 – 12), 60%, 100% and 100% of the rats given 10, 30 and 50 mg/kg of methadone, respectively died during following dosing; there were no deaths in rats given 150 mg/kg of noribgaine alone. The methadone LD_{50} was 68.24 mg/kg (confidence interval 63.58 - 73.25 mg/kg), 29.70 mg/kg (confidence interval 25.65 - 34.38 mg/kg), and 8.86 mg/kg (confidence interval 3.49 - 22.51 mg/kg) after 0, 50, and 150 mg/kg of noribogaine, respectively. Thus the data show that an interaction exists between methadone and noribogaine such that the lethality of methadone is increased when given with noribogaine.

Animal Disposition, Physical Examinations, Cageside, and Postdose Observations

Noribogaine

[0089] Following administration of noribogaine the following were observed: slight ataxia, salivation (slight or severe), and hunched posture. These observations persisted for up to 4 hours following dosing with a greater percentage of animals with observations of ataxia and salivation following a 150 mg/kg dose of noribogaine than at a dose of 50 mg/kg (60-70% versus 30-40%, respectively). The observations of ataxia and salivation were considered to be adverse because they indicate a potential effect on the central nervous system (CNS) In addition to the observation of salivation, ataxia, and hunched posture a few animals exhibited languid behavior and tremors involving the entire body approximately 5 hours following noribogaine at 50 mg/kg which are potentially CNS-related and adverse. Salivation, languid behavior, and ataxia were also noted approximately 5 hours following noribogaine at 150 mg/kg and a single animal exhibited rapid respirations. However, there were no observations of body tremors.

Methadone

[0090] Observations of slight ataxia, salivation, hunched posture, and languid behavior occurred within one hour following administraton of methadone alone at doses of 10 and 30 mg/kg. The ataxia, salivation and languid behavior indicate a potential effect on the central nervous system and are adverse, and the ataxia and languid behavior are expected pharmacological effects of an opiate. Following administration of methadone alone at 50 mg/kg the animals became prostrate, had tremors, shallow respirations, and in some cases were severely languid with hunched posture. These observations were adverse because they are indicative of opiate overdosage and because mortality occurred in one animal 55 min following the dose of methadone at 50 mg/kg.

Methdone with noribogaine

[0091] Methadone when administered at 10 mg/kg following noribogaine at 50 mg/kg resulted in ataxia, languid behavior, salivation, and hunched posture at incidence rates similar to controls which were not dosed with methadone. Increasing the methadone dose to 30 mg/kg

resulted in the same observations but also resulted in observations of labored breathing, prostration, and stiffening of the body (most likely catalepsy). Mortality also occurred that was not observed following administration of methadone alone at this dose. The frequency of these observations (including mortality) increased following noribogaine at 50 mg/kg and methadone at 50 mg/kg when compared to administration of methadone alone 50 mg/kg.

[0092] Administration of methadone at 10 mg/kg following noribogaine at 150 mg/kg resulted in ataxia, languid behavior, salivation, and hunched posture at incidence rates that were greater than that of controls which were not dosed with methadone, and there was an increase in mortality. Increasing the dose of methadone to 30 mg/kg also resulted in observations of ataxia, languid behavior, salivation, and hunched posture at incidence rates that were greater than that of controls which were not dosed with methadone but were also greater than in animals dosed with noribogaine at 150 mg/kg followed by methadone at 10 mg/kg. In addition, observations of labored breathing, prostration, tremors of the whole body, and mortality also occurred that were not observed following methadone alone at 10 mg/kg. The frequency of these observations following methadone at 50 mg/kg following noribogaine at 150 mg/kg was similar to that following methadone at 30 mg/kg when given after 150 mg/kg of noribogaine.

[0093] Adverse observations associated with administration of noribogaine alone persisted for approximately 6.5 to 7 hours following dosing which correlates with the reported long half-life of noribogaine following oral administration. Observations of slight languid behavior persisted through 1.75 hours following administration of methadone alone at 10 mg/kg but adverse observations associated with methadone at doses of 30 and 50 mg/kg persisted through 3 hours following the methadone dose. Following noribogaine at 50 mg or 150 mg/kg and methadone at 10, 30, and 50 mg/kg adverse observations resolved over times similar to those observed for noribogaine when given alone at doses of 50 and 150 mg/kg.

CONCLUSIONS

[0094] The purpose of the study was to evaluate the potential adverse effects that may result when noribogaine (test article) was administered orally prior to the oral administration of methadone (interaction article) to male Sprague Dawley rats.

[0095] This study tested oral doses of 50 and 150 mg/kg noribogaine (as noribogaine hydrochloride); the doses were selected based on the data supplied by the Sponsor. The noribogaine dose was administered 4 h ± 0.5 h prior to administration of methadone which is within the range corresponding to the T_{max} of oral noribogaine in rats. Methadone oral doses of 10, 30, and 50 mg/kg were administered to facilitate detection of possible potentiating effects of noribogaine on methadone lethality.

[0096] In conclusion, slight ataxia, salivation (slight or severe), and hunched posture occurred following noribogaine doses of 50 and 150 mg/kg. Observations of slight ataxia, salivation, hunched posture, and languid behavior occurred when methadone alone was given at doses of 10 and 30 mg/kg and prostration, tremors, and shallow respirations were observed following a methadone dose of 50 mg/kg. Dose-dependent mortality occurred at methadone doses of 30 and 50 mg/kg. When methadone was administered following administration of noribogaine there was a dose-dependent increase in severity and frequency of ataxia, languid behavior, salivation, labored/shallow respirations, prostration, and hunched posture, and the appearance body stiffening (possibly catalepsy), and a dose-dependent increase in mortality. The methadone LD_{50} was 68.24 mg/kg (confidence interval 63.58 - 73.25 mg/kg), 29.70 mg/kg (confidence interval 25.65 - 34.38 mg/kg), and 8.86 mg/kg (confidence interval 3.49 - 22.51 mg/kg) after 0, 50, and 150 mg/kg of noribogaine, respectively. These data show that oral administration of noribogaine at doses of 50 and 150 mg/kg potentiates the mortality associated with oral administration of methadone. Accordingly, there is a negative interaction between methadone and noribogaine such that the lethality of methadone is increased when given with noribogaine.

EXAMPLE 2: HUMAN CLINICAL TRIAL

[0097] The safety, tolerability and pharmacokinetics of noribogaine in opioid dependent participants seeking to discontinue their methadone OST (opioid substitution treatment) is performed as follows.

[0098] The tolerability, pharmacokinetic and pharmacodynamic assessments and an assessment of various secondary efficacy outcome measures are conducted in 3 cohorts of 9

participants, aged 18 to 55 years old who are receiving methadone OST (30mg to 80mg/day) and are seeking to discontinue methadone OST. In each cohort, participants are randomized to study treatment which will be either a single dose of noribogaine (6 participants per cohort) or placebo (3 participants per cohort).

[0099] Noribogaine is administered as the hydrochloride salt in gelatin capsules, with microcrystalline cellulose as filler. The dose of noribogaine is adjusted for the additional weight of the HCl moiety.

[0100] The first cohort receives a single dose of 60mg noribogaine. Subsequent cohorts receive ascending single doses of 120, and 240 mg, depending on agreement of a blinded DSMB review of data from the previously completed cohorts. Upon completion of each cohort, all data to Day 4 are collated and analyzed. The DSMB reviews these data as described in the Blinded Dose Level Review Section 11.5.1. The decision to go to the next higher dose level is based on DSMB recommendations.

[0101] Safety assessments, neurological and withdrawal scales, including the Handelsman-Kanof OOWS (objective opiate withdrawal scale), SOWS (subjective opiate withdrawal scale)and the COWS (clinical opiate withdrawal scale)are conducted at specified time-points during screening, enrolment and follow-up periods. These assessments evaluate participant safety, tolerability, pharmacokinetics and pharmacodynamics of noribogaine and demonstrate that noribogaine has an effect on opioid withdrawal. During the screening and enrolment periods, qualified study staff review the risks of opioid detoxification with participants and will seek feedback on their understanding of those risks. Prior to randomization to study drug, participants complete a seven day methadone washout period, beginning on Day -7. During the washout period, the participant's usual methadone dose is withheld and oral Controlled Release (CR morphine will be given at a 1:4 ratio (methadone : morphine) and divided into two daily doses for six days to participants in an out-patient clinic. The Investigator or designated Sub-Investigator adjusts the CR morphine dose to between a 1:3 and 1:5 ratio according to participant response with the goal of suppressing objective evidence of opioid withdrawal when reviewed just prior to the morning dose on Day -7 to Day -1. Drugs of abuse screening and breath alcohol assessments will be conducted prior to each CR morphine dosing. While in residence at the Clinical Site on Day -1 an oral Immediate Release IR morphine dose equaling 50% of the

participant's Day -2 CR morphine dose is given in six divided doses at 0800, 1100, 1400, 1700, 2000 and 2300 to minimize peak-trough fluctuations. Supplemental IR or CR morphine is given as needed. The final morphine dose of 20mg is given at 0600 on Day 1. All participants who withdraw or are withdrawn from the study prior to receiving randomized study drug are restarted on oral methadone and medically managed according to the Practice Guidelines for Opioid Substitution Treatment. On Day 1 randomized study drug (placebo or noribogaine) is given at approximately 0800. The Investigator or Sub Investigator manages participant withdrawal by prescribing non opioid treatment at discretion.

[0102] During treatment, noribogaine safety and tolerability is evaluated with the following clinicial signs:

1) Adverse Events

2) Vital signs (heart rate, respiration rate, blood pressure, temperature)

3) ECG parameters including QT, QTc

4) Ophthalmological examination

5) Laboratory tests (haematology, biochemistry, and urinalysis

6) C-SSRS

[0103] Noribogaine Pharmacokinetics is monitored for the patient to confirm the blood dose of noribogaine. Urine levels of noribogaine and its metabolites are assayed from collections beginning at time of randomized study drug administration and ending at 0800 on Day **4**. Samples will be taken at 0 (pre-dose), 6, 12, 24, 36, 48 and 72 hours.

Successful withdrawal is demonstrated by a combination of clinical signs.

1. ability to discontinue methadone a longer time than normal before OST resumes
2. Suppression of the withdrawal effects, as shown by SOWS, OOWS, COWS, Mood VAS and ASI assessments
3. Safety and tolerability are monitored by Adverse Events

- Vital signs (heart rate, respiration rate, blood pressure, temperature)
- ECG parameters including QT, QTc
- Ophthalmological examination

- Laboratory tests (haematology, biochemistry, and urinalysis)
- C-SSRS

4. The number of requests and doses of nicotine replacement gum, eCigarettes and nicotine lozenges ST,

[0104] Patients who request resumption of OST within 24 hours of randomised dosing (when noribogaine levels may still be elevated), are given an initial dose of oral CR morphine 20mg. Additional CR morphine is given to suppress objective symptoms of withdrawal. On Day 2 when noribogaine blood levels near trough, the patient is switched to oral methadone. Patients whose initial request for OST is on Day 2 or later are administered oral methadone. Supplemental doses of CR morphine are given at the Investigator's discretion until withdrawal suppression has been established.

[0105] Post discharge from the Clinical Site, patients are seen in the Clinical Site daily for 3 consecutive days, and on two non consecutive days during the next two weeks. Patients are followed via telephone on non clinic visit days at specified time-points to assess the participant's safety and well being. After day 35, patients are followed for resumption of addictive behavior.

[0106] A patient who has not restarted methadone by Day 7 is considered to have been treated successfully with noribogaine. Such a patient is therefore suitable for further treatments with noribogaine if methadone use or other addiction reoccurs.

[0107] The foregoing clinical protocol provides guidance for the treatment of a person who is currently being administered methadone.

[0108] The person of ordinary skill will understand that this protocol may be adapted according to the clinical judgment of treating staff.

What is claimed is:

1. A method for treating addiction in a mammal being administered methadone, the method comprising: (a) cessation of methadone administration to the mammal for a period of time until the serum level of methadone is reduced to a level that is safe to administer noribogaine; (b) administration of noribogaine or a noribogaine derivative to the mammal.

2. The method of claim 1, wherein all or substantially all of the methadone is removed from the serum of the patient.

3. The method of claim 1, further comprising measuring the level of methadone or methadone metabolites in a bodily fluid from the mammal.

4. The method of claim 1, further comprising administration of a non-methadone opioid concurrently with cessation of methadone.

5. The method of claim 4, wherein the non-methadone opioid is morphine

6. The method of claim 5, wherein the morphine is an extended release morphine

7. The method of claim 4, wherein the cessation of methadone administration occurs through a gradual reduction in the dose or frequency of administration of methadone.

8. The method of claim 1, wherein the period of time is at least 200 hours.

9. The method of claim 1, wherein the noribogaine or noribogaine derivative is noribogaine.

10. A method for treating addiction in a mammal, comprising: (a) determining the presence of methadone in the mammal; (b) wherein, in a mammal positive for methadone, treating the mammal to reduce the level of methadone until all or substantially all of the methadone is removed; (c) to a mammal negative or from whom all or substantially all of the methadone is removed, administration of noribogaine or a noribogaine derivative.

11. A method for treating addiction in a mammal, comprising: (a) determining in the mammal, the presence of a drug with potential for a negative interaction with noribogaine; (b) in a mammal positive for the presence of the drug, treating the mammal to reduce the level of the drug until all or substantially all of the drug is removed (c) to a mammal negative for the drug, or from whom all or substantially all of the drug is removed, administering noribogaine or a noribogaine derivative.

12. The method of claim 11, wherein the drug with potential for a negative interaction with noribogaine is methadone.

13. The method of claim 11, wherein, prior to administration of noribogaine, the mammal patient is placed in a controlled environment until the level of noribogaine in the mammal is substantially zero.

14. The method claim 11, wherein the mammal is administered morphine as a substitute for other opioids.

15. A method of treating addiction in a mammal, comprising (a) administering noribogaine to the mammal (b) monitoring the presence of noribogaine in the mammal (c) preventing exposure to drugs other than morphine until all or substantially all of the noribogaine in the mammal is removed

16. A method of treating the behavioural phase of addiction in a mammal, comprising (a) administering noribogaine to the mammal (b) monitoring the presence of noribogaine in the mammal (c) preventing exposure to drugs other than morphine,

wherein the administering noribogaine to the mammal occurs at a dose that is from 5-50% of the dose required for treating acute the acute phase of addiction.

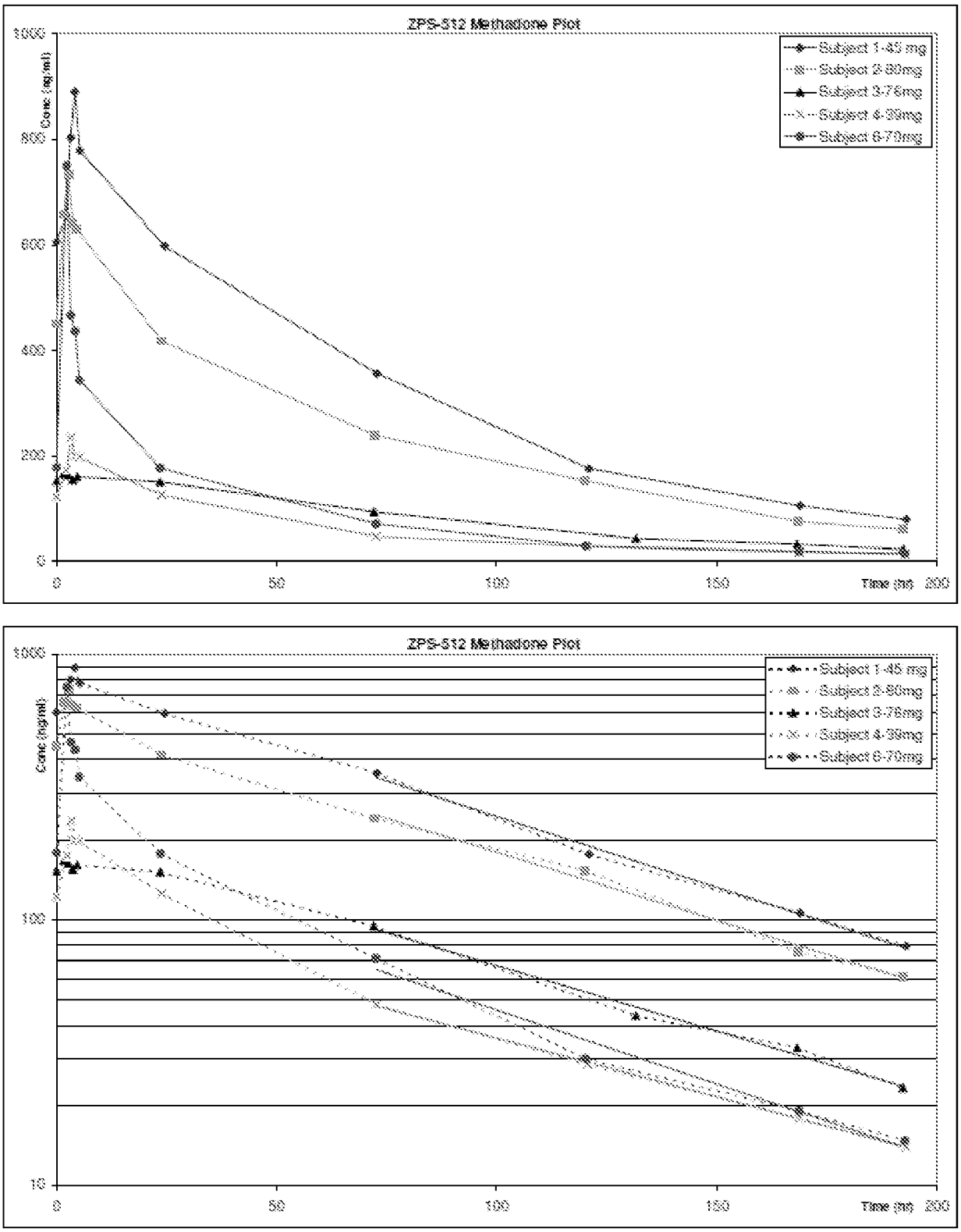
17. A method for pretreating an opioid addicted patient undergoing methadone therapy such that the patient qualifies for noribogaine therapy to treat the underlying opioid addiction, comprises maintaining the patient on a methadone abstinence regimen until sufficient methadone has been removed from the patient's serum thereby allowing said patient to

undergo noribogaine therapy.

18. The method of claim 17, further comprising administering morphine to the patient.

19. A method for treating addiction in an opioid addicted patient undergoing methadone therapy which method comprises confirming that a sufficient amount of methadone has been removed from the patient's serum and then administering a therapeutic amount of noribogaine, a noribogaine derivative or a pharmaceutically acceptable salt thereof to said patient under conditions wherein the patient is no longer opioid addicted.

Figure 1


ZPS-512 Methadone Plot
Conc (ng/ml)
Time (hr)
Subject 1-45 mg
Subject 2-90mg
Subject 3-75mg
Subject 4-30mg
Subject 6-70mg
ZPS-512 Methadone Plot
Conc (ng/ml)
Time (hr)
Subject 1-45 mg
Subject 2-90mg
Subject 3-75mg
Subject 4-30mg
Subject 6-70mg

INTERNATIONAL SEARCH REPORT

PCT/US 13/69235

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/55; A61P 25/36 (2014.01)
USPC - 514/214.02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) -A61K 31/55; A61P 25/36 (2014.01)
USPC - 514/214.02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 540/579, 514/282, 648-649

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase (pgpb, uspt, usoc, epab, jpab, dwpi, tdbd), Dialog Proquest (npl), Google Patents (pl, npl), Google scholar (pl, npl); Search Terms: Noribogaine, ibogaine, methadone, morphine, addict, treat, opioid, opiate, serum, plasma, blood, level, concentration, amidone, heptadone, hydroxyibogamine, hour, withdrawal, extended, sustained, release, zero

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/0083485 A1 (MASH) 05 April 2012 (05.04.2012) entire document, especially para [0007], [0010], [0017], [0026], [0029]	1-19
Y	DONNELLY, "The need for ibogaine in drug and alcohol addiction treatment." The Journal of legal medicine, 2011, Vol.32, pp 93-114.	1-9, 11-19
Y	CALSYN, et al. "Slow tapering from methadone maintenance in a program encouraging indefinite maintenance." Journal of substance abuse treatment, 2006, Vol.30, pp 159-163.	10
Y	EAP, et al. "Interindividual variability of the clinical pharmacokinetics of methadone." Clinical pharmacokinetics, 2002, Vol.41(14), pp 1153-1193.	3, 8, 11-14
Y	US 2003/0194438 A1 (PRESCOTT, et al.) 16 October 2003 (16.10.2003) entire document, especially para [0002], [0023]-[0024]	4-7, 14-16, 18

☐ Further documents are listed in the continuation of Box C. ☐

* 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
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 February 2014 (15.02.2014)	10 MAR 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774