Provided are methods of treating patients suffering from or susceptible to at least one symptom of abuse of, dependence on, or withdrawal from at least one substance with nepicastat in combination with psychosocial therapy. Also provided are methods of treating at least one phase of substance dependence on at least one substance in patients and certain methods of treating at least one phase of cocaine dependence in patients.
METHODS FOR TREATING DEPENDENCE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Application No. 61/171,552, filed April 22, 2009, the entire disclosure of which is hereby incorporated by reference in its entirety for all purposes.

FIELD

[0002] The invention relates to the use of dopamine β-hydroxylase (DBH) inhibitors for the treatment of substance addiction and modification of behavior associated with substance addiction. In particular, the invention relates to methods of treating patients with nepicastat in combination with psychosocial therapy.

BACKGROUND

[0003] Substance abuse and dependence are characterized by substance craving, seeking, and use with loss of control in limiting intake of the substance. These behaviors occur despite significant substance use related problems and at the expense of other behaviors. In 2004, approximately 22.5 million Americans aged 12 or older needed treatment for substance (alcohol or illicit drug) abuse. In 2002, the estimated cost to society of illicit drug abuse was $181 billion.

[0004] The problem of cocaine abuse and dependence is a major medical, social, and legal concern. According to the 2005 National Survey on Drug Use and Health, approximately 13.9% of Americans aged 12 and older have tried cocaine at least once in their lifetimes and 3.3% have tried crack cocaine at least once in their lifetimes. More troublesome, in 2005, there were 2.4 million persons who were current cocaine users, which is greater than in 2004 when the number was 2.0 million. Similarly, the number of current crack users increased from 467,000 in 2004 to 682,000 in 2005. In 2004, the Drug Abuse Warning Network estimated 940,953 drug-related emergency room visits nationwide, and cocaine was involved in the majority of these.

[0005] Present therapies used to treat cocaine addicts have several limitations leading to a very high rate of recidivism. First, and perhaps most fundamentally, the neurochemical events in cocaine abuse and addiction are complex, and as a result, single acting neuropharmacological approaches, such as inhibition of dopamine uptake, do not appear to be
sufficient to overcome addiction. Second, the drugs currently used in addiction treatments have significant side-effects themselves, limiting their utility. Third, drug therapy compliance is problematic among this patient population. Current therapies can require frequent visits to a health care provider and/or self-administration of drugs designed to cure the addict of his habit. Because many of these drugs prevent the euphoria associated with cocaine, there is a strong disincentive to taking the drug. Fourth, because of the complex chemistries involved in pharmacological therapies, many of them may be incompatible with other therapies currently in use or in clinical trials. Finally, most of the pharmacotherapy studies have been administered as outpatient treatment programs and have not been linked with psychosocial treatment.

Clearly, there is a need for a broadly effective treatment approach, and one including a medication component may be more effective than current behavioral treatments such as cognitive behavioral therapy or contingency management alone.

Cognitive behavioral therapy offers benefit to some patients and little or none to others. In the last 30 years, there has been significant progress in the development and validation of psychosocial treatments for substance abuse and dependence, with a predominant focus on the validation of cognitive behavioral treatments. Prominent among these approaches have been contingency management interventions and interventions emphasizing functional analyses and strategies for changing higher-risk situations for drug use in either relapse prevention or other cognitive behavioral formats.

Based on principles of operant conditioning, contingency management interventions offer incentives or rewards to encourage specific behavior goals. In the case of treatments for substance dependence, monetary and nonmonetary rewards typically have been made contingent on negative toxicology screens, indicating abstinence from drug use. Success has been variable as judged by relapse rates.

An alternative approach, relapse prevention, focuses on identifying and intervening with higher-risk situations or events for drug use by helping individuals either avoid or manage these situations by rehearing alternative (nondrug) responses.

However, little is known about how the broad range of psychosocial treatments compare to one another across different outcome variables (e.g., abstinence, dropout rate, etc.), and even less is known about the overall strength of psychosocial treatments across different drugs of abuse. In addition, the effect of contingency management on cocaine use...
reduction can be transient and can have variable results that can depend on the therapist. Thus, psychosocial therapy alone is not effective in treating or preventing drug abuse.

[0011] In addition to psychosocial therapy, a variety of pharmacological treatments have been studied in clinical trials, without noteworthy success. In particular, numerous randomized controlled clinical trials of antidepressants have been completed, including trials of desipramine, fluoxetine, bupropion, and imipramine. Clinical trials of mood stabilizers, including carbamazepine and lithium have also been completed, as have trials of phenytoin, direct or indirect dopamine agonists, including bromocriptine, pergolide, amantadine, mazindole, and methylphenidate. A range of other agents, including ritanserin, geprione, nimodipine, and naltrexone have been studied as well. None of these compounds has proved reliably efficacious. Several medications acting on GABA systems have been evaluated as treatments for cocaine dependence, including tiagabine, baclofen, and vigabatrin. Results for tiagabine have been equivocal, those for baclofen have been slightly more encouraging, though not compelling. Studies of vigabatrin have been perhaps equally encouraging, though based primarily on open-label trials. The outcomes from these development efforts have generally been discouraging.

[0012] The dopamine β-hydroxylase (DBH) inhibitor disulfiram is the most effective pharmacologic treatment for cocaine dependence currently available. Unfortunately, disulfiram non-specifically inhibits several enzymes, including aldehyde dehydrogenase and plasma esterases. Disulfiram and related compounds chelate copper, which is a necessary cofactor for a variety of enzymes, including aldehyde dehydrogenase, plasma esterases and DBH. By inhibiting aldehyde dehydrogenase, disulfiram alters the metabolism of alcohol (ethanol), producing the disulfiram-ethanol reaction. This reaction consists of flushing, nausea, and hypotension.

[0013] Inhibition of plasma esterases slows the elimination of cocaine, which can result in elevations in plasma cocaine levels. In laboratory studies evaluating effects of intranasal cocaine during treatment with disulfiram, disulfiram treatment markedly increased plasma cocaine levels. Increased cocaine levels were not associated with alterations in physiologic or subjective effects of cocaine, however. Six-fold elevations in plasma cocaine levels were observed in one controlled study, and greater elevations may occur in the context of uncontrolled illicit use. A subsequent study using IV cocaine dosing documented that disulfiram slowed the elimination of cocaine, presumably by inhibiting plasma esterases.
Slow absorption following intranasal dosing accounted for the increases in plasma concentrations observed earlier.

[0014] Several studies have shown preliminary efficacy of disulfiram as a treatment of cocaine dependence. In human laboratory studies, treatment with disulfiram reduced the positive subjective effects produced by cocaine. Patients with comorbid alcohol and cocaine dependence had improved outcomes when treated with disulfiram, up to 500 mg. Similarly, buprenorphine-maintained opiate- and cocaine-dependent patients reduced cocaine use during treatment with disulfiram. Recently, results from a large clinical trial suggested that disulfiram 250 mg per day was associated with reduced cocaine use compared to placebo, regardless of alcohol use pattern or type of psychotherapy provided. In this study, 112 cocaine-dependent volunteers were randomized to placebo or disulfiram, and provided one of two psychotherapies. Disulfiram treatment was associated with reduced cocaine use documented by the provision of fewer cocaine-positive urine samples compared to placebo treatment. The effect size was modest and this outcome remains to be replicated.

[0015] Disulfiram inhibits DBH, the single enzyme that mediates the synthesis of norepinephrine (NE). DBH is expressed in noradrenergic neurons and is localized within synaptic vesicles and is released along with NE. DBH can be measured in the plasma, and the concentration of DBH is highly heritable and variability in activity is largely accounted for by variability at the DBH locus. The T variant (-1021C→T) is associated with diminished DBH gene transcription and with lower DBH activity. This allele is fairly common. The frequency of the T allele is reported to be 20% among African-Americans, 22% among Northern European Americans and 16% among Japanese. The corresponding haplotype frequencies are 0.32, 0.34, and 0.09 for these populations, respectively.

[0016] Several reports indicate that disulfiram is more effective in patients with lower DBH activity. It has been shown that in subjects with low DBH activity, the proportion of cocaine-positive urines decreased over time during treatment with disulfiram 250 mg/day relative to placebo but significantly increased over time during treatment with 62.5 mg and 125 mg disulfiram/day (p's < 0.04). In those with high DBH activity, the proportion of cocaine-positive urines increased over time with disulfiram at 62.5 mg/day relative to placebo (p=0.001). Thus, the efficacy of 250 mg/day disulfiram treatment appears limited to those with low DBH activity, which corresponds to the C→T genotype. Doses of disulfiram lower than 250 mg/day appear to increase cocaine use, possibly by reducing cocaine clearance by inhibiting plasma esterases, thus increasing the abuse-related euphoric effects of cocaine.
Disulfiram more effectively reduces cocaine use in patients with the DBH C→T genotype associated with lower DBH activity. Presumably, disulfiram more completely inhibits DBH in those with lower DBH activity, so that disulfiram is more effective in those with the lower activity C→T genotype. The observation that disulfiram is more effective in patients with the low-activity DBH C→T genotype confirms that inhibition of DBH is a key mechanism of action for disulfiram as a therapy for cocaine dependence.

While disulfiram provides a proof-of-concept that DBH inhibitors are promising treatments for cocaine dependence, the usefulness of disulfiram itself as a treatment for cocaine dependence is severely limited by its interactions with alcohol and cocaine.

SUMMARY

Provided are methods of treating patients suffering from or susceptible to at least one symptom of abuse, dependence on, or withdrawal from at least one substance. The methods include administering to the patient a therapeutically effective amount of nepicastat and psychosocial therapy.

Also provided are methods of treating at least one phase of substance dependence on at least one substance in a patient, in which the at least one phase is selected from acquisition, maintenance, extinction, and relapse. The methods include administering to the patient a therapeutically effective amount of nepicastat and psychosocial therapy.

Also provided are methods of treating at least one phase of cocaine dependence in a patient, in which the at least one phase is selected from acquisition, maintenance, extinction, and relapse. The methods include administering to the patient a therapeutically effective amount of nepicastat and psychosocial therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a table with the affinities (IC50s or PKi) of nepicastat with DBH and a range of selected enzymes and receptors.

Fig. 2 shows the details of the individual enzymatic assays.

Fig. 3 shows the effect size achieved with sample sizes ranging from 5 to 15.
DETAILED DESCRIPTION

[0025] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0026] As used herein "nepicastat" includes (S)-5-Aminomethyl-l-(5,7-difluoro-1,2,3,4-tetrahydronaphth-2-yl)-2,3-dihydro-2-thioxo-lH-imidazole, (i?)-5-Aminomethyl-l-(5,7-difluoro-1,2,3,4-tetrahydronaphth-2-yl)-2,3-dihydro-2-thioxo-lH-imidazole, and mixtures thereof, as well as pharmaceutically acceptable salts thereof, such as the hydrochloride salt. In some embodiments nepicastat ((5)-5-Aminomethyl-l-(5,7-difluoro-1,2,3,4-tetrahydronaphth-2-yl)-2,3-dihydro-2-thioxo-lH-imidazole hydrochloride) is used.

[0027] As used herein, "Compound B" refers to (i?)-5-Aminomethyl-l-(5,7-difluoro-1,2,3,4-tetrahydronaphth-2-yl)-2,3-dihydro-2-thioxo-lH-imidazole, as well as pharmaceutically acceptable salts thereof, such as the hydrochloride salt.

[0028] "Pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, such as hydrochlorate, phosphate, diphosphate, hydrobromate, sulfate, sulfinate, nitrate, and like salts; as well as salts with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluencesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate such as acetate, HOOC-(CH2)n-COOH where n is 0-4, and like salts.

[0029] In addition, if a compound is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

[0030] The term "patient," as used herein, refers to a mammal. In certain embodiments, the term "patient" refers to a human.

[0031] The terms "administer," "administering," or "administration," as used herein, refer to either directly administering nepicastat or a composition thereof to a patient.
The terms "treat" or "treating," as used herein, refers to partially or completely alleviating, inhibiting, preventing, ameliorating and/or relieving the condition, or at least one symptom thereof.

The terms "suffer" or "suffering" as used herein refers to one or more conditions that a patient has been diagnosed with, or is suspected to have.

The term "susceptible" as used herein refers to having a likelihood of being affected by at least one symptom of a condition.

Those of ordinary skill in the art will appreciate that "substance abuse" often involves symptoms of physical and/or psychological "dependence." Also, when the substance of abuse is withdrawn from a dependent individual, the individual often develops certain symptoms including sleep and mood disturbance and intense craving of the substance of abuse, known as "withdrawal." The methods described herein encompass treatment of substance abuse itself, dependence, and also of withdrawal.

The term "substance abuse," as used herein, can be defined with reference to criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Text revision (2000) ("DSM-IV TR"), which was prepared by the Task Force on DSM-IV of the American Psychiatric Association. A feature of substance abuse is a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances. As recited in the DSM-IV TR, substance abuse is defined as maladaptive pattern of substance abuse leading to clinically significant impairment or distress, as manifested by at least one of the following symptoms, occurring within a 12-month period: (1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home; (2) recurrent substance use in situations in which it is physically hazardous; (3) recurrent substance-related legal problems; and (4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance. In addition, the DSM-IV TR requires that the symptoms of substance abuse have never met the criteria for substance dependence. In some embodiments, treatment of substance abuse with nepicstat reduces the amount or frequency of substance use in a patient. In some embodiments, treatment of substance abuse with nepicstat in a patient reduces at least one DSM-IV TR symptom for substance abuse. In some embodiments, treatment with nepicstat in a patient reduces at least one symptom of substance abuse which includes by way of example and without limitation at least one of
euphoria, apathy, irritability, recklessness, poor judgment, compulsion, aggression, anger, craving for the substance being abused, and mood disorders. In some embodiments, treatment with nepicastat reduces the substance craving induced by a stressful event in a patient.

[0037] As used herein, the phrase "reduces a symptom" refers to reducing at least one of the frequency and amplitude of a symptom of a condition in a patient. In certain embodiments the patient enters remission and no longer experiences the symptom.

[0038] As used herein, the phrase "increases a symptom" refers to increasing at least one of the frequency and amplitude of a symptom of a condition in a patient.

[0039] The term "substance dependence," as used herein, can be defined with reference to criteria set forth in the DSM-IV TR. The symptoms for substance dependence set forth in DSM-IV TR is a pattern of substance use, leading to clinically significant impairment or distress as manifested by at least three selected from the following group, occurring at any time within the same twelve month period: (1) tolerance as defined by either (a) a need for substantially increased amounts of the substance to achieve the desired effect; or (b) substantially diminished effect with continued use of the same amount of the substance; (2) withdrawal, as demonstrated by either (a) the characteristic withdrawal syndrome for the specific substance; or (b) the same, or a closely related substance is taken to relieve or avoid withdrawal symptoms; (3) the substance is often taken in larger amounts or over a longer period than was intended; (4) there is a persistent desire or unsuccessful efforts to cut down or control substance use; (5) a great deal of time is spent in activities to obtain the substance, use the substance, or recover from its effects; (6) important social, occupational or recreational activities are given up or reduced because of substance use; and (7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. Substance dependence can be with physiological dependence, where evidence of tolerance or withdrawal is present, or without physiological dependence, where no evidence of tolerance or withdrawal is present. In some embodiments, nepicastat treatment of substance dependence reduces the amount or frequency of substance use by a patient. In some embodiments, nepicastat treatment of substance dependence reduces at least one DSM-IV TR symptom for substance dependence in a patient. In some embodiments, treatment with nepicastat in a patient reduces at least one symptom of substance dependence which includes by way of example and without limitation at least one of euphoria, apathy, irritability,
recklessness, poor judgment, compulsion, aggression, anger, craving for the substance depended upon, and mood disorders. In some embodiments, treatment with nepicatstat reduces the substance craving induced by a stressful event in a patient.

[0040] As used herein, "remission" refers to a state during which the occurrence of at least one symptom of substance abuse or dependence has been reduced. In some embodiments, the term remission does not apply if the patient is on agonist therapy or in a controlled environment where access to the relevant substance is restricted. In some embodiments remission refers to a state during which the occurrence of at least one symptom of substance abuse or dependence does not occur. In some embodiments, remission refers to a state during which all symptoms of substance abuse or dependence have been reduced in a patient. In some embodiments, remission refers to a state during which no symptoms of substance abuse or dependence occur. In some embodiments, remission refers to a state during which substance use does not occur.

[0041] In some embodiments, the remission is characterized by at least one of early full remission, early partial remission, sustained full remission, and sustained partial remission and only applies after none of the symptoms for substance abuse and dependence have been present for at least one month. The definition of these four types of remission are based on the interval of time that has elapsed since the cessation of dependence (early versus sustained remission) and whether there is continued presence of at least one symptom of substance dependence or abuse (partial versus full remission).

[0042] The qualifier "early full remission" is used when for at least one month, but for less than twelve months, no symptom of substance dependence or substance abuse has been met.

[0043] The qualifier "early partial remission" is used when for at least one month but less than 12 months, at least one symptom of substance dependence or substance abuse has been met, but the criteria for substance dependence or substance abuse have not been met.

[0044] The term "sustained full remission" is used when none of the symptoms of substance dependence or substance abuse have been met at any time during a period of at least twelve months.

[0045] The term "sustained partial remission" is used when for at least twelve months, at least one symptom of substance dependence or substance abuse has been met, but the criteria for substance dependence or substance abuse have not been met.
In some embodiments, nepicastat treatment promotes remission in a patient. In some embodiments, nepicastat treatment prolongs a period of remission period in a patient.

The phrase "prolong a period of remission" refers to increasing the interval of time during which the patient is in remission. In some embodiments, a stressful event can cause remission to end in a patient. In some embodiments, relapse occurs at the end of remission. In some embodiments, nepicastat treatment reduces the likelihood that remission will end in a patient after a stressful event. In some embodiments, nepicastat treatment promotes at least one of early partial remission, sustained full remission, sustained partial remission, and sustained full remission.

"Withdrawal" refers to a collection of symptoms that arise when administration of a relevant substance is reduced, delayed, or stopped. The substance-specific symptoms of withdrawal can cause clinically significant distress or impairment in social, occupational or other important areas of functioning, for example. These symptoms are not due to a general medical condition and are not better accounted for by another mental disorder. Withdrawal usually, but not necessarily, is associated with substance dependence. In some embodiments, treatment with nepicastat reduces at least one symptom of withdrawal in a patient. In some embodiments, withdrawal symptoms include for example and without limitation apathy, irritability, recklessness, poor judgment, compulsion, aggression, anger, substance craving, mood disorders, and sleep disorders. In some embodiments, treatment with nepicastat reduces the substance craving induced by a stressful event in a patient.

The term substance dependence can be characterized by the presence of at least one of the following conditions characterized in the DSM-IV TR: Alcohol Abuse; Alcohol Dependence; Alcohol Intoxication; Alcohol Intoxication Delirium; Alcohol Withdrawal; Alcohol Withdrawal Delirium; Alcohol-Induced Anxiety Disorder; Alcohol-Induced Mood Disorder; Alcohol-Induced Persisting Amnestic Disorder; Alcohol-Induced Persisting Dementia; Alcohol-Induced Psychotic Disorder, With Delusions; Alcohol-Induced Psychotic Disorder, With Hallucinations; Alcohol-Induced Sexual Dysfunction; Alcohol-Induced Sleep Disorder; Alcohol-Related Disorder Not Otherwise Specified (NOS); Amphetamine Abuse; Amphetamine Dependence; Amphetamine Intoxication; Amphetamine Intoxication Delirium; Amphetamine Withdrawal; Amphetamine-Induced Anxiety Disorder; Amphetamine-Induced Mood Disorder; Amphetamine-Induced Psychotic Disorder, With Delusions; Amphetamine-Induced Psychotic Disorder, With Hallucinations; Amphetamine-Induced Sexual Dysfunction; Amphetamine-Induced Sleep Disorder; Amphetamine-Related Disorder NOS;
Cannabis Abuse; Cannabis Dependence; Cannabis Intoxication Delirium; Cannabis-Induced Anxiety Disorder; Cannabis-Induced Psychotic Disorder, With Delusions; Cannabis-Induced Psychotic Disorder, With Hallucinations; Cannabis-Related Disorder NOS; Cocaine Abuse; Cocaine Dependence; Cocaine Intoxication Delirium; Cocaine Withdrawal; Cocaine-Induced Anxiety Disorder; Cocaine-Induced Mood Disorder; Cocaine-Induced Psychotic Disorder, With Delusions; Cocaine-Induced Psychotic Disorder, With Hallucinations; Cocaine-Induced Sexual Dysfunction; Cocaine-Induced Sleep Disorder; Cocaine-Related Disorder NOS; Inhalant Abuse; Inhalant Dependence; Inhalant Intoxication; Inhalant Intoxication Delirium; Inhalant-Induced Anxiety Disorder; Inhalant-Induced Mood Disorder; Inhalant-Induced Persisting Dementia; Inhalant-Induced Psychotic Disorder, With Delusions; Inhalant-Induced Psychotic Disorder, With Hallucinations; Inhalant-Related Disorder NOS; Opioid Abuse; Opioid Dependence; Opioid Intoxication; Opioid Intoxication Delirium; Opioid Withdrawal; Opioid-Induced Mood Disorder; Opioid-Induced Psychotic Disorder, With Delusions; Opioid-Induced Psychotic Disorder, With Hallucinations; Opioid-Related Disorder NOS; Phencyclidine Abuse; Phencyclidine Dependence; Phencyclidine Intoxication; Phencyclidine Intoxication Delirium; Phencyclidine-Induced Anxiety Disorder; Phencyclidine-Induced Mood Disorder; Phencyclidine-Induced Psychotic Disorder, With Delusions; Phencyclidine-Induced Psychotic Disorder, With Hallucinations; and Phencyclidine-Related Disorder NOS.

The terms "cessation" and "withdrawal" may be, but need not be, in reference to the following conditions characterized in the DSM-IV TR: Nicotine Withdrawal; Nicotine-Related Disorder Not otherwise Specified; Nicotine Dependence, with physiological dependence; Nicotine Dependence, without physiological dependence; Nicotine Dependence, Early Full Remission; Nicotine Dependence, Early Partial Remission; Nicotine Dependence, Sustained Full Remission; Nicotine Dependence, Sustained Partial Remission; Nicotine Dependence, On Agonist Therapy; Opioid Withdrawal; Opioid-Related Disorder Not Otherwise Specified; Opioid Dependence, with physiological dependence; Opioid Dependence, without physiological dependence; Opioid Dependence, Early Full Remission; Opioid Dependence, Early Partial Remission; Opioid Dependence, Sustained Full Remission; Opioid Dependence, Sustained Partial Remission; Opioid Dependence On Agonist Therapy; and Opioid Dependence in a controlled environment; Ethanol Withdrawal; Ethanol Dependence with Physiological Dependence; Ethanol Withdrawal, without Physiological
Dependence; Ethanol Withdrawal, Early Full Remission; Ethanol Withdrawal, Early Partial Remission; Ethanol Withdrawal, Sustained Full Remission; Ethanol Withdrawal, Sustained Partial Remission; Ethanol Withdrawal, on Agonist Therapy; Ethanol Withdrawal, In a Controlled Environment; Amphetamine Withdrawal; and Cocaine Withdrawal.

[0051] As used herein, "on agonist therapy" refers to being treated with an agonist for substance abuse, dependence, or withdrawal. The term "agonist" refers to a factor including, but not limited to a chemical compound, such as a small molecule or a complex organic compound or a protein, that triggers a response in a patient that is at least one response or partial response of the substance being abused, depended upon, or withdrawn from by the patient. For example, in some embodiments, "Opioid Dependence on Agonist Therapy" refers to Opioid Dependence on methadone therapy.

[0052] Withdrawal symptoms can arise upon reduction of any of a variety of substances. For example, the discontinued use of tobacco products, all of which contain nicotine, typically results in the onset of nicotine withdrawal conditions. Individuals often suffer the symptoms of nicotine withdrawal as a consequence of the discontinued use of tobacco in any form, including, but not limited to smoking of cigarette, cigar, or pipe tobacco, or the oral or intranasal ingestion of tobacco or chewing tobacco. Such oral or intranasal tobacco includes, but is not limited to snuff and chewing tobacco. The cessation of nicotine use or reduction in the amount of nicotine use, is often followed within 24 hours by symptoms including dysphoria, depressed mood; light-headedness; insomnia; irritability, frustration or anger; anxiety; nervous tremor; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain; and the craving for tobacco or nicotine. These symptoms often cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The methods described herein may be used to alleviate one or more symptoms attributed to nicotine withdrawal when such symptoms are not due to a general medical condition and are not better accounted for by another medical disorder. The present method is also helpful to those who have replaced, or partially replaced, their use of tobacco with the use of nicotine replacement therapy. Thus, such patients can be assisted to reduce and even eliminate entirely their dependence on nicotine in all forms.

[0053] The discontinuing or reduction in administration of an opioid, typically self-administration, through injection or orally, through smoking or intranasal ingestion, often results in the presence of a characteristic opioid withdrawal condition. This withdrawal condition can also be precipitated by administration of an opioid antagonist such as naloxone
or naltrexone after opioid use. Opioid withdrawal is characterized by symptoms that are generally opposite to the opioid agonist effects. These withdrawal symptoms may include anxiety; restlessness; muscle aches, often in the back and legs; craving for opioids; irritability and increased sensitivity to pain; dysphoric mood; nausea or vomiting; lacrimation; rhinorrhoea; papillary dilation; piloerection; sweating; diarrhea; yawning; fever; and insomnia. When dependence is on short-acting opioids, such as heroin, withdrawal symptoms usually occur within 6-24 hours after the last dose, while with longer-acting opioids, such as methadone, symptoms may take 2-4 days to emerge. These symptoms often cause clinically significant distress or impairment in social, occupational or other important areas of functioning. The methods described herein can be used to alleviate one or more symptoms attributed to opioid withdrawal when such symptoms are not due to a general medical condition and are not better accounted for by another medical disorder.

[0054] The discontinuing of or reduction in use of ethanol (e.g., ethanol containing beverages) results in the onset of ethanol withdrawal conditions. Ethanol withdrawal conditions are characterized by symptoms that begin when blood concentrations of ethanol decline sharply, i.e., within 4 to 12 hours after ethanol use has been stopped or reduced. These ethanol withdrawal symptoms include craving for ethanol; autonomic hyperactivity (such as sweating or pulse rate greater than 100); hand tremor; insomnia; nausea; vomiting; transient visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety; and grand mal seizures. These symptoms often cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The methods described herein may be used to alleviate one or more symptoms attributed to ethanol withdrawal when such symptoms are not due to a general medical condition and are not better accounted for by another medical disorder.

[0055] Cocaine abuse and dependence can cause cognitive, behavioral, and physiological symptoms. Symptoms of cocaine abuse and dependence can include varying degrees of attention deficit hyperactivity disorder and euphoria; increased energy, excitement, and sociability; less hunger and fatigue; a marked feeling of physical and mental strength; dysphoria; decreased sensation of pain; and craving for cocaine. Respiratory effects include symptoms such as bronchitis, shortness of breath, and chest pain, and cardiovascular effects include symptoms such as heart palpitations, arrhythmia, cardiomyopathy, and heart attacks. Symptoms also include dilated pupils, nausea, vomiting, headache, vertigo, anxiety, dizziness, psychosis, and confusion. Administration of cocaine through snorting or sniffing
can result in ear, nose, and throat effects including nasal irritation, nasal crusting, recurrent nosebleeds, nasal stuffiness, and facial pain. In some embodiments, nepicastat treatment reduces at least one symptom of cocaine abuse and dependence in a patient. In some embodiments, nepicastat treatment increases at least one negative subjective symptom of cocaine abuse and dependence.

[C0056] Cocaine withdrawal symptoms can include a fatigue, lack of pleasure, depression, irritability, sleep disorders, increased appetite, psychomotor retardation, agitation, extreme suspicion, and craving for cocaine. In some embodiments, nepicastat treatment reduces at least one symptom of cocaine withdrawal.

[C0057] Substance dependence can be characterized by the phases: acquisition, maintenance, extinction, and relapse. As used herein, the term "acquisition" refers to a phase of substance dependence in which dependence on the substance is initiated and acquired by a patient. In some embodiments, nepicastat treatment inhibits the development of the acquisition phase in a patient. In some embodiments, nepicastat treatment of the acquisition phase reduces at least one of the amount or frequency of substance use by a patient. In some embodiments, nepicastat treatment of the acquisition phase reduces at least one DSM-IV symptom of substance abuse and dependence in a patient. In some embodiments, nepicastat treatment of the acquisition phase reduces at least one symptom of substance abuse and dependence which include by way of example and without limitation at least one of euphoria, apathy, irritability, recklessness, poor judgment, compulsion, aggression, anger, craving for the substance being abused or depended upon, and mood disorders. In some embodiments, treatment with nepicastat reduces the substance craving induced by a stressful event in a patient during the acquisition phase.

[C0058] "Maintenance" refers to a phase of substance dependence in which there is stable administration to or use of the substance by a patient. In some embodiments, a 10% variance in at least one of the amount and frequency of substance use by a patient is considered a stable behavior. In some embodiments, nepicastat treatment of the maintenance phase reduces at least one of the amount and frequency of substance use by a patient. In some embodiments, nepicastat treatment of the maintenance phase reduces at least one DSM-IV symptom of substance abuse and dependence in a patient. In some embodiments, nepicastat treatment of the maintenance phase reduces at least one symptom of substance abuse and dependence which includes by way of example and without limitation at least one of euphoria, apathy, irritability, recklessness, poor judgment, compulsion, aggression, anger,
craving for the substance being abused or depended upon, and mood disorders. In some embodiments, treatment with nepicastat reduces the substance craving induced by a stressful event in a patient during the maintenance phase.

[0059] "Extinction" refers to a phase of substance dependence in which the substance is not provided to a patient or a patient abstains from use of the substance. In some embodiments, the dependence on the substance is extinguished or reduced in the extinction phase. In some embodiments, at least one withdrawal symptom occurs in the extinction phase. In some embodiments, nepicastat treatment promotes the development of the extinction phase in a patient. In some embodiments, nepicastat treatment of the extinction phase reduces at least one DSM-IV symptom of substance abuse and dependence in a patient. In some embodiments, nepicastat treatment during the extinction phase reduces at least one symptom of substance abuse and dependence which includes by way of example and without limitation at least one of euphoria, apathy, irritability, recklessness, poor judgment, compulsion, aggression, anger, craving for the substance being abused or depended upon, and mood disorders. In some embodiments, nepicastat treatment reduces the withdrawal symptoms in a patient in the extinction phase. In some embodiments, treatment with nepicastat reduces the substance craving induced by a stressful event in a patient in the extinction phase.

[0060] "Relapse" refers to recurrence of at least one symptom of substance abuse or dependence after a period of abstinence in a patient. In some embodiments, the relapse occurs at the end of remission. In some embodiments, a patient has undergone extinction training prior to relapse. In some embodiments, relapse occurs after drug priming, stress, or exposure to an environment related cue or stimulation that was previously associated with substance use. In some embodiments, nepicastat treatment reduces the frequency of relapse in a patient. In some embodiments, nepicastat treatment of the relapse phase reduces at least one DSM-IV symptom of substance abuse and dependence in a patient. In some embodiments, nepicastat treatment of the relapse phase reduces at least one symptom of substance abuse and dependence which includes by way of example and without limitation at least one of euphoria, apathy, irritability, recklessness, poor judgment, compulsion, aggression, anger, craving for the substance being abused or depended upon, and mood disorders. In some embodiments, nepicastat treatment reduces the withdrawal symptoms in a patient during the relapse phase. In some embodiments, treatment with nepicastat reduces the substance craving induced by a stressful event in a patient during the relapse phase.
[0061] The term "psychotic" as used herein refers to a psychiatric condition in its broadest sense, including hallucinations, a loss of ego boundaries, a gross impairment in reality testing, impairment with the capacity to meet ordinary demands of life, delusions, any prominent hallucinations, disorganized speech, or disorganized or catatonic behavior, and the like.

[0062] The term "psychosis" refers to a psychiatric symptom, condition or syndrome in its broadest sense, and can refer to a symptom associated with a general medical condition, a disease state or other condition, such as a side effect of drug abuse (a substance-induced disorder) or as a side effect of a medication. Psychosis includes a mental disorder or condition causing gross distortion or disorganization of a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others to the degree of interfering with his capacity to cope with the ordinary demands of everyday life.

[0063] Treatment of substance abuse, dependence, and withdrawal may be conducted in stages. In some embodiments, an initial period of abstinence from substance use is preferred before induction of treatment with nepicastat in a patient. In some embodiments, an initial low dose of nepicastat is administered to a patient. In some embodiments, the amount of nepicastat administered to a patient is escalated until a desired therapeutic response is observed. In some embodiments, the amount of nepicastat is escalated in order to determine the optimal dose to treat the condition while minimizing symptoms, side effects, and cravings for the substance in a patient.

[0064] In some embodiments, nepicastat treatment promotes remission. In some embodiments, the dose of nepicastat is unchanged or tapered off after remission is reached in a patient.

[0065] Provided are methods of treating a patient suffering from or susceptible to at least one symptom of abuse of, dependence on, or withdrawal from at least one substance. The methods include administering to the patient a therapeutically effective amount of nepicastat. In some embodiments, the at least one substance is selected from a drug of abuse and a medication. In some embodiments, the drug of abuse is selected from a psychostimulant agent, an opioid, a hallucinogen, an inhalant, a sedative, a tranquilizer, a hypnotic, an anxiolytic, and an illicit substance. In some embodiments, the psychostimulant agent is a beta-phenylisopropylamine derivative. In some embodiments, the beta-phenylisopropylamine derivative is selected from amphetamine, dextroamphetamine, and
methamphetamine. In some embodiments, the psychostimulant agent is selected from ecstasy, phenmetrazine, methylphenidate, diethylpropion, pemoline, mazindol, (-) cathione, and fenfluramine. In some embodiments, the opioid is selected from Lortab, Tramadol, heroin, methadone, hydrocodone, and oxycodone. In some embodiments, the hallucinogen is selected from psilocybin, a hallucinogenic mushroom, lysergic acid diethylamide (LSD), phencyclidine (PCP), and ketamine. In some embodiments, the inhalant is selected from benzene, toluene, o-xylene, m-xylene, p-xylene, ethylbenzene, fluorobenzene, o-difluorobenzene, 1,3,5-trifluorobenzene, 1,2,4-trifluorobenzene, pentafluorotoluene, pentafluorobenzene, and perfluorobenzene. In some embodiments, the medication is selected from an anesthetic, an analgesic, an anticholinergic agent, an antihistamine, a muscle relaxant, a nonsteroidal anti-inflammatory medication, an over the counter medication, and an antidepressant medication. In some embodiments, the drug of abuse is cocaine, alcohol, caffeine, opium, cannabinoid, cannabis, benzodiazapine carisprodol, tobacco, nicotine, Vicodin, Lorcan, Percocet, Percodan, and Tylox. In some embodiments, the drug of abuse is cocaine and nepicastat reduces at least one symptom of cocaine abuse and dependence in the patient selected from attention deficit hyperactivity disorder; euphoria; increased energy, excitement and sociability; less hunger and fatigue; a marked feeling of physical and mental strength; decreased sensation of pain; bronchitis; shortness of breath; chest pain; heart palpitations; arrhythmia; cardiomyopathy; heart attack; dilated pupils; nausea; vomiting; headache; vertigo; dizziness; anxiety; psychosis; confusion; nasal irritation; nasal crusting; recurrent nosebleeds; nasal stuffiness; facial pain; dysphoria; and craving for cocaine.

[0066] In some embodiments, the drug of abuse is cocaine and nepicastat increases at least one negative subjective symptom of cocaine abuse and dependence. In some embodiments, the drug of abuse is cocaine and nepicastat reduces at least one symptom of cocaine withdrawal selected from fatigue, lack of pleasure, depression, irritability, sleep disorders, increased appetite, psychomotor retardation, agitation, extreme suspicion, and craving for cocaine. In some embodiments, nepicastat treatment improves a score of the patient on at least one of the attention deficit hyperactivity disorder IV rating scale (ADHD-IV), Hamilton Depression Scale (HAM-D), Hamilton Anxiety Scale (HAM-A), Beck Depression inventory (BDI), apathy scale from Neuropsychiatric Inventory, and a cognitive function rating scale. In some embodiments, the cognitive function rating scale is selected from the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Wechsler Memory Scale-
Revised (WMS-R), Rey Auditory Verbal Learning Test (RAVLT, Trials I-VII), Rey Complex Figure Test (RCFT), and the Trail Making Test (TMT, Parts A and B).

[0067] In some embodiments, nepicastat reduces in the patient at least one of the amount and frequency of substance use by the patient. In some embodiments, nepicastat reduces in the patient at least one symptom of abuse of, dependence on, or withdrawal from the at least one substance. In some embodiments, nepicastat reduces at least one symptom of substance abuse in the patient selected from recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home; recurrent substance use in situations in which it is physically hazardous; recurrent substance-related legal problems; and continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance. In some embodiments, nepicastat reduces at least one symptom of substance dependence in the patient selected from tolerance; withdrawal; the substance is often taken in larger amounts or over a longer period then was intended; there is a persistent desire and/or unsuccessful efforts to cut down or control substance use; a great deal of time is spent in at least one of activities to obtain the substance, use the substance, and recover from its effects; at least one of important social, occupational and recreational activities are given up and/or reduced because of substance use; and the substance use is continued despite knowledge of having a persistent and/or recurrent physical and/or psychological problem that is likely to have been caused or exacerbated by the substance.

[0068] In some embodiments, nepicastat promotes remission in the patient. In some embodiments, the remission is characterized by at least one of early full remission, early partial remission, sustained full remission, and sustained partial remission. In some embodiments, nepicastat prolongs a period of remission in the patient. In some embodiments, the methods further include treatment with at least one of contingency management and cognitive behavioral therapy.

[0069] In some embodiments, the methods further include co-administering a therapeutically effective amount of least one other agent selected from a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), a norepinephrine reuptake inhibitor (NRI), a norepinephrine-dopamine reuptake inhibitor (NDRI), a serotonin 5-hydroxytryptamine1A (5HT1A) antagonist, a dopamine β-hydroxylase inhibitor, an adenosine receptor antagonist, an adenosine A2A receptor antagonist, a monoamine oxidase inhibitor (MAOI), a monoamine oxidase B inhibitor, a sodium channel blocker, a calcium channel blocker, a central and peripheral alpha adrenergic receptor
antagonist, a central alpha adrenergic agonist, a central or peripheral beta adrenergic receptor antagonist, a NK-I receptor antagonist, a corticotropin releasing factor (CRF) antagonist, an atypical antidepressant/antipsychotic, a tricyclic, an anticonvulsant, a glutamate antagonist, a gamma-aminobutyric acid (GABA) agonist, a GABA metabolism enzyme inhibitor, a GABA synthesis activator, a partial dopamine D2 agonist, a dopamine metabolism enzyme inhibitor, a catechol-O-methyl-transferase inhibitor, an opioid receptor antagonist, a mood stabilizer, a direct or indirect dopamine agonist, a partial 5HT1 agonist, a serotonin 5HT2 agonist, an opioid, a carboxylase inhibitor, a partial opioid agonist, a partial nicotinic agonist, and an inhalant.

[0070] In some embodiments, the at least one other agent is a SSRI selected from paroxetine, sertraline, citalopram, escitalopram, and fluoxetine. In some embodiments, the at least one other agent is a SNRI selected from duloxetine, mirtazapine, and venlafaxine. In some embodiments, the at least one other agent is a NRI selected from bupropion and atomoxetine. In some embodiments, the at least one other agent is the NDRI bupropion. In some embodiments, the at least one other agent is the dopamine β-hydroxylase inhibitor disulfiram. In some embodiments, the at least one other agent is the adenosine A2A receptor antagonist istradefylline. In some embodiments, the at least one other agent is a sodium channel blocker selected from lamotrigine, carbamazepine, oxcarbazepine, and valproate. In some embodiments, the at least one other agent is a calcium channel blocker selected from nimodipone, lamotrigine, and carbamazepine. In some embodiments, the at least one other agent is the central and peripheral alpha adrenergic receptor antagonist prazosin. In some embodiments, the at least one other agent is the central alpha adrenergic agonist clonidine. In some embodiments, the at least one other agent is the central or peripheral beta adrenergic receptor antagonist propranolol. In some embodiments, the at least one other agent is an atypical antidepressant/antipsychotic selected from bupropion, olanzepine, risperidone, and quetiapine. In some embodiments, the at least one other agent is a tricyclic selected from amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protiptyline, and trimipramine. In some embodiments, the at least one other agent is an anticonvulsant selected from phenytoin, lamotrigine, carbamazepine, oxcarbazepine, valproate, topiramate, tiagabine, vigabatrin, and levetiracetam. In some embodiments, the at least one other agent is the glutamate antagonist topiramate. In some embodiments, the at least one other agent is a GABA agonist selected from baclofen, valproate, and topiramate. In some embodiments, the at least one other agent is the dopamine metabolism enzyme inhibitor carbidopa. In some
embodiments, the at least one other agent is the partial dopamine D2 agonist aripiprazole. In some embodiments, the at least one other agent is an opioid receptor antagonist selected from naltrexone and naloxone. In some embodiments, the at least one other agent is a mood stabilizer selected from carbamazepine and lithium. In some embodiments, the at least one other agent is a direct or indirect dopamine agonist selected from dopamine, bromocriptine, pergolide, amantadine, mazindole, and methylphenidate. In some embodiments, the at least one other agent is the partial 5HT1 agonist gepirone. In some embodiments, the at least one other agent is the serotonin 5HT2 antagonist ritanserin. In some embodiments, the at least one other agent is the opioid methadone. In some embodiments, the at least one other agent is the partial opioid agonist buprenorphine. In some embodiments, the at least one other agent is the partial nicotinic agonist champix. In some embodiments, the at least one other agent is an inhalant selected from benzene, toluene, o-xylene, m-xylene, p-xylene, ethylbenzene, fluorobenzene, o-difluorobenzene, 1,3,5-trifluorobenzene, 1,2,4-trifluorobenzene, pentafluorotoluene, pentafluorobenzene, and perfluorobenzene. In some embodiments, the methods further include co-administering a therapeutically effective amount of at least one other agent selected from benzodiazepine, levodopa, carisprodol, modafinil, acamprosate, gamma-butyrolactone, gamma-hydroxybutyrate, opium, psilocybin, hallucinogenic mushroom, tobacco, and nicotine.

[0071] In some embodiments, nepicastat is administered to the patient after a period of abstinence from substance use by the patient. In some embodiments, the therapeutically effective amount of nepicastat in the patient is determined by escalating the amount of nepicastat administered to the patient until a desired therapeutic response is observed. In some embodiments, the amount of nepicastat is tapered off after remission is reached in the patient. In some embodiments, the amount of nepicastat is unchanged after remission is reached in the patient.

[0072] Also provided are methods of treating at least one phase of substance dependence on at least one substance in a patient. In some embodiments, the at least one phase of substance dependence is selected from acquisition, maintenance, extinction, and relapse. The methods include administering to the patient a therapeutically effective amount of nepicastat. In some embodiments, nepicastat inhibits the development of the acquisition phase in the patient. In some embodiments, nepicastat promotes the development of the extinction phase in the patient. In some embodiments, nepicastat reduces the frequency of relapse in the patient. In some embodiments, the at least one substance is selected from a drug of abuse and
a medication. In some embodiments, the drug of abuse is selected from a psychostimulant agent, an opioid, a hallucinogen, an inhalant, a sedative, a tranquilizer, a hypnotic, an anxiolytic, and an illicit substance. In some embodiments, the psychostimulant agent is a beta-phenylisopropylamine derivative. In some embodiments, the beta-phenylisopropylamine derivative is selected from amphetamine, dextroamphetamine, and methamphetamine. In some embodiments, the psychostimulant agent is selected from ecstasy, phenmetrazine, methylphenidate, diethylpropion, pemoline, mazindol, (-) cathione, and fenfluramine. In some embodiments, the opioid is selected from Lortab, Tramadol, heroin, methadone, hydrocodone, and oxycodone. In some embodiments, the hallucinogen is selected from psilocybin, a hallucinogenic mushroom, lysergic acid diethylamide (LSD), phencyclidine (PCP), and ketamine. In some embodiments, the inhalant is selected from benzene, toluene, o-xylene, m-xylene, p-xylene, ethylbenzene, fluorobenzene, o-difluorobenzene, 1,3,5-trifluorobenzene, 1,2,4-trifluorobenzene, pentafluorotoluene, pentafluorobenzene, and perfluorobenzene. In some embodiments, the medication is selected from an anesthetic, an analgesic, an anticholinergic agent, an antihistamine, a muscle relaxant, a nonsteroidal anti-inflammatory medication, an over the counter medication, and an antidepressant medication. In some embodiments, the drug of abuse is alcohol, caffeine, opium, cannabinoid, cannabis, benzodiazapine, carisprodol, tobacco, nicotine, Vicodin, Loracet, Percocet, Percodan, and Tylox.

[0073] In some embodiments, nepicastat treatment improves a score of the patient on at least one of the ADHD-IV, HAM-D, HAM-A, BDI, apathy scale from Neuropsychiatric Inventory, and a cognitive function rating scale. In some embodiments, the cognitive function rating scale is selected from the WAIS-R, WMS-R, RAVLT, Trials I-VII, RCFT, and TMT, Parts A and B. In some embodiments, nepicastat reduces in the patient at least one of the amount and frequency of use of the at least one substance by the patient. In some embodiments, nepicastat reduces in the patient at least one symptom of abuse of, dependence on, or withdrawal from the at least one substance. In some embodiments, nepicastat reduces at least one symptom of substance abuse in the patient selected from recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home; recurrent substance use in situations in which it is physically hazardous; recurrent substance-related legal problems; and continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance. In some embodiments, nepicastat reduces at least one symptom of substance dependence in the patient
selected from tolerance; withdrawal; the substance is often taken in larger amounts or over a longer period then was intended; there is a persistent desire and/or unsuccessful efforts to cut down or control substance use; a great deal of time is spent in at least one of activities to obtain the substance, use the substance, and recover from its effects; at least one of important social, occupational and recreational activities are given up and/or reduced because of substance use; and the substance use is continued despite knowledge of having a persistent and/or recurrent physical and/or psychological problem that is likely to have been caused or exacerbated by the substance.

[0074] In some embodiments, nepicastat promotes remission in the patient. In some embodiments, the remission is characterized by at least one of early full remission, early partial remission, sustained full remission, and sustained partial remission. In some embodiments, nepicastat prolongs a period of remission in the patient. In some embodiments, the methods further include treatment with at least one of contingency management and cognitive behavioral therapy.

[0075] In some embodiments, the methods further include co-administering a therapeutically effective amount of at least one other agent selected from a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), a norepinephrine reuptake inhibitor (NRI), a norepinephrine-dopamine reuptake inhibitor (NDRI), a serotonin 5-hydroxytryptamine1A (5HT1A) antagonist, a dopamine β-hydroxylase inhibitor, an adenosine receptor antagonist, an adenosine A2a receptor antagonist, a monoamine oxidase inhibitor (MAOI), a monoamine oxidase B inhibitor, a sodium channel blocker, a calcium channel blocker, a central and peripheral alpha adrenergic receptor antagonist, a central alpha adrenergic agonist, a central or peripheral beta adrenergic receptor antagonist, a NK-I receptor antagonist, a corticotropin releasing factor (CRF) antagonist, an atypical antidepressant/antipsychotic, a tricyclic, an anticonvulsant, a glutamate antagonist, a gamma-aminobutyric acid (GABA) agonist, a GABA metabolism enzyme inhibitor, a GABA synthesis activator, a partial dopamine D2 agonist, a dopamine metabolism enzyme inhibitor, a catechol-O-methyl-transferase inhibitor, an opioid receptor antagonist, a mood stabilizer, a direct or indirect dopamine agonist, a partial 5HT1 agonist, a serotonin 5HT2 antagonist, an opioid, a carboxylase inhibitor, a partial opioid agonist, a partial nicotinic agonist, and an inhalant. In some embodiments, the at least one other agent is a SSRI selected from paroxetine, sertraline, citalopram, escitalopram, and fluoxetine. In some embodiments, the at least one other agent is a SNRI selected from duloxetine, mirtazapine, and venlafaxine. In
some embodiments, the at least one other agent is a NRI selected from bupropion and atomoxetine. In some embodiments, the at least other agent is the NDRI bupropion. In some embodiments, the at least one other agent is the dopamine β-hydroxylase inhibitor disulfiram. In some embodiments, the at least one other agent is the adenosine A2A receptor antagonist istradefylline. In some embodiments, the at least one other agent is a sodium channel blocker selected from lamotrigine, carbamazepine, oxcarbazepine, and valproate. In some embodiments, the at least one other agent is a calcium channel blocker selected from nimodopone, lamotrigine, and carbamazepine. In some embodiments, the at least one other agent is the central and peripheral alpha adrenergic receptor antagonist prazosin. In some embodiments, the at least one other agent is the central alpha adrenergic agonist clonidine. In some embodiments, the at least one other agent is the central or peripheral beta adrenergic receptor antagonist propranolol. In some embodiments, the at least one other agent is an atypical antidepressant/antipsychotic selected from bupropion, olanzepine, risperidone, and quetiapine. In some embodiments, the at least one other agent is a tricyclic selected from amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptiyline, protpiptyline, and trimipramine. In some embodiments, the at least one other agent is an anticonvulsant selected from phenytoin, lamotrigine, carbamazepine, oxcarbazepine, valproate, topiramate, tiagabine, vigabatrin, and levetiracetam. In some embodiments, the at least one other agent is the glutamate antagonist topiramate. In some embodiments, the at least one other agent is a GABA agonist selected from baclofen, valproate, and topiramate. In some embodiments, the at least one other agent is the dopamine metabolism enzyme inhibitor carbidopa. In some embodiments, the at least one other agent is the partial dopamine D2 agonist aripiprazole. In some embodiments, the at least one other agent is an opioid receptor antagonist selected from naltrexone and naloxone. In some embodiments, the at least one other agent is a mood stabilizer selected from carbamazepine and lithium. In some embodiments, the at least one other agent is a direct or indirect dopamine agonist selected from dopamine, bromocriptine, pergolide, amantadine, mazindole, and methylphenidate. In some embodiments, the at least other agent is the partial 5HT1 agonist gepirone. In some embodiments, the at least other agent is the serotonin 5HT2 antagonist ritanserin. In some embodiments, the at least other agent is the opioid methadone. In some embodiments, the at least other agent is the partial opioid agonist buprenorphine. In some embodiments, the at least other agent is the partial nicotinic agonist champix. In some embodiments, the at least one other agent is an inhalant selected from benzene, toluene, o-xylene, m-xylene, p-xylene, ethylbenzene, fluorobenzene, o-difluorobenzene, 1,3,5-trifluorobenzene, 1,2,4-trifluorobenzene, pentafluorotoluene,
pentafluorobenzene, and perfluorobenzene. In some embodiments, the methods further include co-administering a therapeutically effective amount of at least one other agent selected from benzodiazepine, levodopa, carisprodol, modafenil, acamprosate, gamma-butyrolactone, gamma-hydroxybutyrate, opium, psilocybin, hallucinogenic mushroom, tobacco, and nicotine.

[0076] In some embodiments, nepicastat is administered to the patient after a period of abstinence from substance use by the patient. In some embodiments, the therapeutically effective amount of nepicastat in the patient is determined by escalating the amount of nepicastat administered to the patient until a desired therapeutic response is observed. In some embodiments, the amount of nepicastat is tapered off after remission is reached in the patient. In some embodiments, the amount of nepicastat is unchanged after remission is reached in the patient.

[0077] Also provided are methods of treating at least one phase of cocaine dependence in a patient. In some embodiments, the at least one phase is selected from acquisition, maintenance, extinction, and relapse. The methods include administering to the patient a therapeutically effective amount of nepicastat. In some embodiments, nepicastat inhibits the development of the acquisition phase in the patient. In some embodiments, nepicastat promotes development of the extinction phase in the patient. In some embodiments, nepicastat reduces the frequency of relapse in the patient. In some embodiments, nepicastat reduces in the patient at least one symptom of abuse of, dependence on, or withdrawal from cocaine. In some embodiments, nepicastat reduces at least one symptom of cocaine abuse in the patient selected from recurrent cocaine use resulting in a failure to fulfill major role obligations at work, school, or home; recurrent cocaine use in situations in which it is physically hazardous; recurrent cocaine-related legal problems; and continued cocaine use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the cocaine. In some embodiments, nepicastat reduces at least one symptom of cocaine dependence in the patient selected from tolerance; withdrawal; the cocaine is often taken in larger amounts or over a longer period then was intended; there is a persistent desire or unsuccessful efforts to cut down or control cocaine use; a great deal of time is spent in activities to obtain the cocaine, use the cocaine, or recover from its effects; important social, occupational or recreational activities are given up or reduced because of cocaine use; and the cocaine use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the cocaine. In
some embodiments, nepicastat reduces at least one symptom of cocaine abuse and
dependence selected from attention deficit hyperactivity disorder; euphoria; increased energy,
excitement and sociability; less hunger and fatigue; a marked feeling of physical and mental
strength; decreased sensation of pain; bronchitis; shortness of breath; chest pain; heart
palpitations; arrhythmia; cardiomyopathy; heart attack; dilated pupils; nausea; vomiting;
headache; vertigo; dizziness; anxiety; psychosis; confusion; nasal irritation; nasal crusting;
recurrent nosebleeds; nasal stuffiness; facial pain; dysphoria; and craving for cocaine. In
some embodiments, nepicastat increases at least one negative subjective symptom of cocaine
abuse and dependence. In some embodiments, nepicastat reduces at least one symptom of
cocaine withdrawal selected from fatigue, lack of pleasure, depression, irritability, sleep
disorders, increased appetite, psychomotor retardation, agitation, extreme suspicion, and
craving for cocaine. In some embodiments, nepicastat improves a score of the patient on at
least one of ADHD-IV, HAM-D, HAM-A, BDI, apathy scale from Neuropsychiatric
Inventory, and a cognitive function rating scale. In some embodiments, the cognitive
function rating scale is selected from WAIS-R, WMS-R, RAVLT, Trials I-VII, RCFT, and
TMT, Parts A and B. In some embodiments, nepicastat reduces at least one of the amount
and frequency of cocaine use by the patient. In some embodiments, nepicastat promotes
remission in the patient.

[0078] In some embodiments, the remission is characterized by at least one of early full
remission, early partial remission, sustained full remission, and sustained partial remission.
In some embodiments, nepicastat prolongs a period of remission in the patient. In some
embodiments, the methods further include treatment with at least one of contingency
management and cognitive behavioral therapy.

[0079] In some embodiments, the methods further include co-administering a
therapeutically effective amount of at least one other agent selected from a selective serotonin
reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), a
norepinephrine reuptake inhibitor (NRI), a norepinephrine-dopamine reuptake inhibitor
(NDRI), a serotonin 5-hydroxytryptamine1A (5HT1A) antagonist, a dopamine β-hydroxylase
inhibitor, an adenosine receptor antagonist, an dopamine A2A receptor antagonist, a
monoamine oxidase inhibitor (MAOI), a monoamine oxidase B inhibitor, a sodium channel
blocker, a calcium channel blocker, a central and peripheral alpha adrenergic receptor
antagonist, a central alpha adrenergic agonist, a central or peripheral beta adrenergic receptor
antagonist, a NK-I receptor antagonist, a corticotropin releasing factor (CRF) antagonist, an
atypical antidepressant/antipsychotic, a tricyclic, an anticonvulsant, a glutamate antagonist, a
gamma-aminobutyric acid (GABA) agonist, a GABA metabolism enzyme inhibitor, a GABA
synthesis activator, a partial dopamine D2 agonist, a dopamine metabolism enzyme inhibitor,
a catechol-O-methyl-transferase inhibitor, an opioid receptor antagonist, a mood stabilizer, a
direct or indirect dopamine agonist, a partial 5HT1 agonist, a serotonin 5HT2 antagonist, an
opioid, a carboxylase inhibitor, a partial opioid agonist, a partial nicotinic agonist, and an
inhalant. In some embodiments, the at least one other agent is a SSRI selected from
paroxetine, sertraline, escitalopram, and fluoxetine. In some embodiments, the at least
one other agent is a SNRI selected from duloxetine, mirtazapine, and venlafaxine. In
some embodiments, the at least one other agent is a NRI selected from bupropion and
atomoxetine. In some embodiments, the at least other agent is the NDRI bupropion. In some
embodiments, the at least one other agent is the dopamine β-hydroxylase inhibitor disulfiram.
In some embodiments, the at least one other agent is the adenosine A2A receptor antagonist
istradefylline. In some embodiments, the at least one other agent is a sodium channel blocker
selected from lamotrigine, carbamazepine, oxcarbazepine, and valproate. In some
embodiments, the at least one other agent is a calcium channel blocker selected from
nimodopone, lamotrigine, and carbamazepine. In some embodiments, the at least one other
agent is the central and peripheral alpha adrenergic receptor antagonist prazosin. In some
embodiments, the at least one other agent is the central alpha adrenergic agonist clonidine. In
some embodiments, the at least one other agent is the central or peripheral beta adrenergic
receptor antagonist propranolol. In some embodiments, the at least one other agent is an
atypical antidepressant/antipsychotic selected from bupropion, olanzepine, risperidone, and
quetiapine. In some embodiments, the at least one other agent is a tricyclic selected from
amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protiptyline, and
trimipramine. In some embodiments, the at least one other agent is an anticonvulsant
selected from phenytoin, lamotrigine, carbamazepine, oxcarbazepine, valproate, topiramate,
tiagabine, vigabatrin, and levetiracetam. In some embodiments, the at least one other agent is
the glutamate antagonist topiramate. In some embodiments, the at least one other agent is a
GABA agonist selected from baclofen, valproate, and topiramate. In some embodiments, the
at least one other agent is the dopamine metabolism enzyme inhibitor carbidopa. In some
embodiments, the at least one other agent is the partial dopamine D2 agonist aripiprazole. In
some embodiments, the at least one other agent is an opioid receptor antagonist selected from
naltrexone and naloxone. In some embodiments, the at least one other agent is a mood
stabilizer selected from carbamazepine and lithium. In some embodiments, the at least one
other agent is a direct or indirect dopamine agonist selected from dopamine, bromocriptine, pergolide, amantadine, mazindole, and methylphenidate. In some embodiments, the at least other agent is the partial 5HT1 agonist gepirone. In some embodiments, the at least other agent is the serotonin 5HT2 antagonist ritanserin. In some embodiments, the at least other agent is the opioid methadone. In some embodiments, the at least other agent is the partial opioid agonist buprenorphine. In some embodiments, the at least other agent is the partial nicotinic agonist champix. In some embodiments, the at least one other agent is an inhalant selected from benzene, toluene, o-xylene, m-xylene, p-xylene, ethylbenzene, fluorobenzene, o-difluorobenzene, 1,3,5-trifluorobenzene, 1,2,4-trifluorobenzene, pentafluorotoluene, pentafluorobenzene, and perfluorobenzene. In some embodiments, the methods further include co-administering a therapeutically effective amount of least one other agent selected from benzodiazeapine, levodopa, carisprodel, modafenil, acamprosate, gamma-butyrolactone, gamma-hydroxybutyrate, opium, psilocybin, hallucinogenic mushroom, tobacco, and nicotine. In some embodiments, nepicastat is administered to the patient after a period of abstinence from cocaine use by the patient. In some embodiments, the therapeutically effective amount of nepicastat in the patient is determined by escalating the amount of nepicastat administered to the patient until a desired therapeutic response is observed. In some embodiments, the amount of nepicastat is tapered off after remission from cocaine dependence is reached in the patient. In some embodiments, the amount of nepicastat is unchanged after remission from cocaine dependence is reached in the patient. In some embodiments, nepicastat treats at least one symptom of abuse of, dependence on, or withdrawal from at least one secondary substance in the patient. In some embodiments, the at least one secondary substance is selected from a drug of abuse and a medication. In some embodiments, the drug of abuse is selected from a psychostimulant agent, an opioid, a hallucinogen, an inhalant, a sedative, a tranquilizer, a hypnotic, an anxiolytic, and an illicit substance. In some embodiments, the psychostimulant agent is a beta-phenylisopropylamine derivative. In some embodiments, the beta-phenylisopropylamine derivative is selected from amphetamine, dextroamphetamine, and methamphetamine. In some embodiments, the psychostimulant agent is selected from ecstasy, phenmetrazine, methylphenidate, diethylpropion, pemoline, mazindol, (-) cathione, and fenfluramine. In some embodiments, the opioid is selected from Lortab, Tramadol, heroin, methadone, hydrocodone, and oxycodone. In some embodiments, the hallucinogen is selected from psilocybin, a hallucinogenic mushroom, lysergic acid diethylamide (LSD), phencyclidine (PCP), and ketamine. In some embodiments, the inhalant is selected from benzene, toluene, o-xylene, m-
xylene, p-xylene, ethylbenzene, fluorobenzene, o-difluorobenzene, 1,3,5-trifluorobenzene, 1,2,4-trifluorobenzene, pentafluorotoluene, pentafluorobenzene, and perfluorobenzene. In some embodiments, the medication is selected from an anesthetic, an analgesic, an anticholinergic agent, an antihistamine, a muscle relaxant, a nonsteroidal anti-inflammatory medication, an over the counter medication, and an antidepressant medication. In some embodiments, the drug of abuse is alcohol, caffeine, opium, cannabinoid, cannabis, benzodiazepine, carisprodol, tobacco, nicotine, Vicodin, Lorcet, Percocet, Percodan, and Tylox.

[0080] In another aspect of the invention, the methods include administering to the patient a therapeutically effective amount of nepicastat in combination with behavioral therapy including contingency management, cognitive behavioral therapy, motivational enhancement therapy, referral to self-help groups, and the like, for the treatment or prevention of drug use.

[0081] In one aspect of the invention, nepicastat is administered in combination with contingency management for the treatment or prevention of drug abuse, in particular cocaine abuse. In contingency management, a contingent relationship is established between a desired response, such as a urine sample that is free of drug metabolites, and the delivery of a positively reinforcing event, such as money or some desired item. The delivery of a reward that is contingent on reduced drug use. Typically, participants in the contingency management group can be required to provide multiple urine samples for testing over a specified period of time and meet with a therapist to review the patients’ treatment with nepicastat. The meetings can provide the patient with a review of the results of the drug test, the delivery of a voucher, if earned; a discussion of how the voucher or accumulated voucher account could be redeemed; and the delivery of the earned items when the vouchers were redeemed, praise and encouragement, and the like. In one aspect, the reward can be a voucher. The patients can receive vouchers (that can be exchanged for various merchandise) when they remain drug-free and in treatment. The vouchers increase in value for cocaine-free urine samples. The combination of nepicastat and contingency management results in a reduction in drug use, such as cocaine use.

[0082] In another aspect of the invention, nepicastat is administered in combination with cognitive behavioral therapy for the treatment or prevention of drug abuse, in particular cocaine abuse. Cognitive behavioral therapy is based on the theory that learning processes play a critical role in the development of drug addiction and that individuals can learn to
identify and correct the undesired behaviors. Cognitive behavioral therapy is focused on intervention and includes a functional analysis of antecedents and consequences to develop strategies to avoid high-risk situations and to identify alternatives to cocaine’s reinforcing effects. It also includes a heavy emphasis on the development of coping skills, and can include counseling for family counseling or vocational counseling, or attending a mutual-aid group. Unlike contingency management, cognitive behavioral therapy does not usually include a voucher component or intervention with the client outside the treatment setting. Treatment with nepicastat and cognitive behavioral therapy can be undertaken concurrently or treatment with nepicastat can be followed with cognitive behavioral therapy.

[0083] In one aspect of the invention, the cognitive behavioral therapy is relapse prevention that facilitates abstinence as well as provides help for people who experience relapse. The relapse prevention approach to the treatment of cocaine addiction consists of a collection of strategies intended to enhance self-control. Specific techniques include exploring the positive and negative consequences of continued use, self-monitoring to recognize drug cravings early on and to identify high-risk situations for use, and developing strategies for coping with and avoiding high-risk situations and the desire to use. Thus, relapse therapy anticipates the problems patients are likely to meet and helps them develop effective coping strategies.

[0084] In another aspect of the invention, nepicastat is administered in combination with the matrix model, the supportive-expressive psychotherapy, individualized drug therapy, motivational enhancement therapy, or combinations thereof, for the treatment or prevention of drug abuse, in particular cocaine abuse. In the matrix model, the learn about issues critical to addiction and relapse, receive direction and support from a trained therapist, become familiar with self-help programs, and are monitored for drug use by testing. The program can include education for family members affected by the addiction. Typically, the therapist functions as teacher and coach, fostering a positive, encouraging relationship with the patient and using that relationship to reinforce positive behavior change.

[0085] The supportive-expressive psychotherapy is a time-limited, focused psychotherapy that provides supportive techniques to help patients feel comfortable in discussing their personal experiences and expressive techniques to help patients identify and resolve interpersonal relationship issues, with an emphasis on the role drug abuse plays in relation to problem feelings and behaviors, and how problems may be solved without recourse to drugs.
The individualized drug counseling focuses directly on reducing or stopping the drug use, and can also address related areas such as illegal activity, family/social relations, employment status, as well as the content and structure of the patient's recovery program. Individualized drug counseling helps the patient develop coping strategies and tools for abstaining from drug use and maintaining abstinence.

The motivational enhancement therapy aims to change the behavior of the patient by helping the patient remain engaged in the treatment program and in stopping drug use. The motivational enhancement therapy typically consists of an initial assessment. Subsequent treatment session can be used to monitor change, review cessation strategies being used, and continue to encourage commitment to change or sustained abstinence.

In another aspect of the invention, nepicastat is administered in combination with behavioral therapy for the treatment or prevention of drug abuse and psychosis associated with drug abuse, in particular cocaine abuse. Psychosis associated with substance abuse or psychosis as a side-effect of medication is ameliorated by the methods of the invention. For example, psychosis is associated with cocaine abuse and addiction. Thus, the DBH inhibitors of the invention, such as nepicastat, can be used as a treatment for cocaine-induced psychosis, optionally in combination with behavioral therapy. In another aspect of the invention, the methods of the invention can treat cannabis-induced chronic psychosis.

Psychosis is typically characterized as a mental disorder or condition causing gross distortion or disorganization of a person's mental capacity, affective response, and capacity to recognize reality, communicate, relate to others to the degree of interfering with his capacity to cope with the ordinary demands of everyday life, and delusions or hallucinations such as, for example, delusions of guilt, delusions one deserves punishment, nihilistic delusions, somatic delusions, or delusions of poverty. Hallucinations, when present in psychotic major depression are usually transient and not elaborate.

A condition or illness involving psychosis can be classified as a "substance-induced" psychotic disorder if there is recent or prolonged substance use, withdrawal from a substance or exposure to a toxin. The criteria used to classify substance-induced psychotic disorder includes history, physical examination or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition, prominent hallucinations or delusions, the disturbance is not better accounted for by another mental disorder, and, the disturbance does not occur exclusively during the course of a delirium.
Criteria to assess and diagnose psychosis associated with drug abuse and drug addiction can be any of proscribed or empirical criteria to diagnose known in the art. Psychosis can be diagnosed by formal psychiatric assessment using, for example, a semi-structured clinical interview. Objective tests can also be used to determine whether an individual is psychotic and to measure and assess the success of the treatment of the patient with nepicastat in combination with psychotherapy.

In one aspect of the invention, the patient can be diagnosed for the symptoms of psychosis associated with drug abuse, treated with nepicastat in combination with psychosocial therapy and the assessment of treatment of psychosis or any psychiatric condition can be objectively assessed using any test known in the art. Thus, for example, the "Wallach Test" that measures the presence and degree of psychosis by evaluating cognitive changes in the individual, such as recognition memory can be used to diagnose and/or assess the treatment of the patient. The Stroop Color and Word Test ("Stroop Test") is another means to objectively determine whether an individual is psychotic and to measure efficacy of treatment. The Stroop Test can differentiate between individuals with psychosis and those without psychosis based on the scores on the test that measures the time it takes to name colors as compared to reading the color names. Individuals with psychosis have statistically significantly lower scores on the Stroop Test than individuals without psychosis. Thus, psychosis and other psychiatric conditions associated with drug abuse and drug addiction can be diagnosed and evaluated using any of the many tests or criteria well-known and accepted in the fields of psychology or psychiatry.

Pharmacologically acceptable derivatives include acids, bases, enol ethers, and esters, esters, hydrates, solvates, and prodrug forms. The derivative is selected such that its pharmacokinetic properties are superior with respect to at least one characteristic to the corresponding neutral agent. Nepicastat may be derivatized prior to formulation.

A therapeutically effective amount of nepicastat or a pharmacologically acceptable derivative may vary widely depending on the severity of the post-traumatic stress disorder, the age and relative health of the subject, the potency of the compound used and other factors. In certain embodiments a therapeutically effective amount is from about 0.1 milligram per kg (mg/kg) body weight per day to about 50 mg/kg body weight per day. In other embodiments the amount is about 1.0 to about 10 mg/kg/day. Therefore, in certain embodiments a therapeutically effective amount for a 70 kg human is from about 7.0 to about 3500 mg/day, while in other embodiments it is about 70 to about 700 mg/day.
invention, the therapeutic amount of nepicastat can be from about 80 mg to about 400 mg, preferably from about 160 mg to about 240 mg.

[0095] One of ordinary skill in the art of treating such diseases will be able to ascertain a therapeutically effective amount of nepicastat for post-traumatic stress disorder without undue experimentation and in reliance upon personal knowledge and the disclosure of this application. In general, by way of example and without limitation, nepicastat will be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can, by way of example and without limitation, take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, nepicastat in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are, by way of example and without limitation, non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound. Such excipient may be, for example, any solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

[0096] Solid pharmaceutical excipients include by way of example and without limitation starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from for example and without limitation water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable solutions, include by way of example and without limitation water, saline, aqueous dextrose and glycols. Compressed gases may be used to disperse the compound in aerosol form. Inert gases suitable for this purpose are by way of example and without limitation nitrogen, carbon dioxide, nitrous oxide, etc.

[0097] The pharmaceutical preparations can by way of example and without limitation, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. In certain embodiments, they can contain still other therapeutically valuable substances. Other suitable pharmaceutical carriers and their formulations are

[0098] The amount of nepicastat in the composition may vary widely depending for example, upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, the final composition will comprise from 10% w to 90% w of the compound, preferably 25% w to 75% w, with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required.

EXEMPLARY ASPECTS

EXAMPLE 1

[0099] The preparation of nepicastat was based upon the chiral reduction of tetralone 3 (available from the AlCl3-catalyzed Friedel-Crafts reaction of 3,5-difluorophenylacetyl chloride with ethylene in CH2Cl2 at -65 °C) under the conditions described by Terashima (LAH, (-)-li?,2S- N-methylephedrine, 2-ethylaminopyridine) to give i?-(+)-tetralol 4a (92-95% ee), that was converted to the i?-(+)-mesylate, followed by reaction with sodium azide afforded a mixture (9:1) of azide and dihydronaphthalene 7. The azide was hydrogenated and the product treated with anhydrous HCl to give 5’-(−)-amine hydrochloride, converted by a Strecker reaction (formaldehyde bisulfite complex and KCN) to 5’-(−)-aminonitrile. Formation of the heterocycle was accomplished by sequential diformylation of aminonitrile followed by subsequent treatment with thiocyanic acid. Competing hydrolysis of the nitrile afforded comparable amounts of the primary amide. Reduction of nitrile to amine (93-96% ee) was accomplished using LAH in THF. The enantiomer (91.6% ee) was available by the same above described route using (+)-1 S,2i?-JV-methylephedrine as a chiral auxiliary in the Terashima reduction of ketone. The absolute configuration of the chiral center was based upon literature precedence of the previously described 5’-(−)-tetralol.

[0100] Melting points were determined on a Uni-Melt Thomas Hoover Capillary Melting Point Apparatus or a Mettler FB 81HT cell with a Mettler FP90 processor and are uncorrected. Mass spectra were obtained with either a Finnigan MAT 8230 (for electron-impact or chemical ionization) or Finnigan MAT TSQ70 (for LSIMS) spectrometer. 1H NMR spectra were recorded on a Bruker ACF300, AM300, AMX300 or EM390 spectrometer and chemical shifts are given in ppm (δ) from tetramethylsilane as internal
standard. IR spectra were recorded on a Nicolet SPC FT-IR spectrometer. UV spectra were recorded on a Varian Cary 3 UV-Visible spectrometer, Leeman Labs Inc. Optical rotations were measured in a Perkin-Elmer Model 141 polarimeter. Chiral HPLC measurements were performed on a Regis Chiral AGP column (4.6 x 100 mm) eluting with 2% acetonitrile-98% 20 mM KH₂PO₄ (pH 4.7) at 1 nL/min at 20 °C.

[0101] 5,7-Difluoro-2-tetralone. SOCl₂ (100 mL) was added in one portion to 3,5-difluorophenylacetic acid (100 g, 0.58 mol) and after stirring for 15 h, the volatiles were evaporated under reduced pressure. The resulting oily acid chloride was dissolved in CH₂Cl₂ (200 mL) and added dropwise to a mechanically stirred suspension of AICl₃ (154 g, 1.16 mol) in CH₂Cl₂ (1.0 L). The stirred suspension was cooled to an internal temperature of -65 °C in a dry ice/acetone bath, and the acid chloride solution was added at such a rate in order to maintain an internal temperature < -60 °C. After the addition was complete, ethylene gas was bubbled through the reaction mixture at a rapid rate for 10 min at -65 °C. The reaction mixture was allowed to warm to 0 °C over 2 h with stirring, and was then cooled to -10 °C and treated with H₂O (500 mL) initially dropwise, followed by rapid addition. The organic layer was separated, washed with brine (100 mL) and dried over MgSO₄. Evaporation under reduced pressure gave a dark oily residue which was distilled in vacuo on a Kugelrohr collecting material boiling between 90-1 10 °C (1.0 to 0.7 mm Hg). The distillate was redistilled at 100-105 °C (0.3 mm Hg) to give the product as a white solid, (73.6 g, 0.40 mol; 70%): mp 46 °C; IR (KBr) 1705 cm⁻¹; ¹H NMR (CDCl₃) δ 2.55 (t, J = 7.5 Hz, 2H), 3.10 (t, J = 7.5 Hz, 2H), 3.58 (s, 2H), 6.70 (m, 2H); MS m/z 182 (M+). Anal. Calcd for C₁₀H₇F₂O: C, 65.93; H, 4.42. Found: C, 65.54; H, 4.42.

[0102] (-)-2-Hydroxy-5,7-difluoro-1,2,3,4-tetrahydronaphthalene. A solution of (-)-2S- N-methylephedrine (81.3 g, 0.454 mol) in anhydrous Et₂O (1.1 L) was added dropwise (45 min) to 1.0 M lithium aluminum hydride (416 mL, 0.416 mol) in Et₂O at a rate sufficient to maintain a gentle reflux. After the addition was complete, the reaction mixture was heated at reflux for 1 h then allowed to cool to room temperature. A solution of 2-ethylaminopyridine (111 g, 0.98 mole) in anhydrous Et₂O (100 mL) was added (45 min) at such a rate as to maintain a gentle reflux. The reaction mixture was heated at reflux for a further 1 h, during which time a light yellow-green suspension appeared. The mixture was cooled to an internal temperature of -65 °C using a dry ice-acetone bath and a solution of 5,7-difluoro-2-tetralone (23.0 g, 126 mmol) in Et₂O (125 mL) was added dropwise at a rate maintaining the internal temperature below -60 °C. After the addition was complete, the
mixture was stirred at -65 °C to -68 °C for 3 h and quenched by the addition of MeOH (100 mL) maintaining the internal temperature below -60 °C. The reaction was stirred for a further 10 min at -65 °C and allowed to warm to approximately -20 °C. A solution of 3N HCl (2 L) was then added at a rate to limit the temperature to <35 °C. After stirring at an increased rate to achieve total dissolution, the layers were separated and the ethereal layer was washed with brine (200 mL) and dried (MgSO₄). The ethereal solution was evaporated under reduced pressure and the residue dissolved in warm Et₂O (20 mL) followed by the addition of hexane (200 mL). The seeded solution was cooled in an ice bath and maintained at 0° C for 1 h whereupon the resulting deposited crystals were collected and dried in vacuo to give the alcohol (10.9 g, 47 %): mp 85 °C; [α]D²⁵ +38.1° (c = 1.83, CHCl₃); 93.4% ee by chiral HPLC: ¹H NMR (CDCl₃) δ 1.70 (br s, IH), 1.76-1.88 (m, 2H), 1.99-2.06 (m, 2H), 2.63-3.08 (m, 3H), 4.15 (m, IH), 6.60 (m, 2H). Anal. Calcd for Ci₀H₁₀F₂O₂: C, 65.21; H, 5.47. Found: C, 65.38; H, 5.42. The spectra for the lS>enantiomer 4b are identical: mp 84-85 °C; [α]D²⁵ -37.8° (c = 1.24, CHCl₃); 92.4% ee by chiral HPLC. Anal. Calcd for Ci₀H₁₀F₂O₂: C, 65.21; H, 5.47. Found: C, 65.47; H, 5.39.

(i?)-(+-)2-Methanesulfonylxy-5,7-difluoro-1,2,3,4-tetraydroanaphthalene. A solution of i?-(+-)-5,7-difluoro-2-tetralol (59.0 g, 320 mmol) and Et₃N (74.2 mL, 53.9 g, 530 mmol) in anhydrous Et₂O (1.78 L) was cooled (-15 °C) using an ice-MeOH bath and treated under argon with stirring with MsCl (37.2 mL, 55.3 g, 480 mmol) over 5-10 min. After 5 h the reaction was complete (as determined by TLC) and water was added to dissolve the solids. A small amount of EtOAc was added to help complete dissolution of the solids. The organic phase was separated and washed sequentially with 1N HCl, aq. NaHCO₃, brine and dried over MgSO₄. Evaporation of the solvent gave an off-white solid (87.1 g, 332 mmol), used directly in the next step. Trituration of a small sample with /-Pr₂O gave an analytical sample: mp 78.8-80.5 °C; [α]D²⁵ +16.8° (c = 1.86, CHCl₃); ¹H NMR δ 2.13-2.28 (m, 2H), 2.78-2.96 (m, 2H), 3.07 (s, 3H), 3.09 (dd, J = 17.1 Hz, 4.7, IH), 3.20 (dd, J = 17.2, 4.7 Hz, IH), 5.20 (m, IH), 6.67 (m, 2H). Anal. Calcd for CnHi₂F₂O₃S: C, 50.37; H, 4.61. Found: C, 50.41; H, 4.64. The spectra for the lS>enantiomer 5b are identical: mp 79.9-80.9 °C; [α]D²⁵ -16.6° (c = 2.23, CHCl₃). Anal. Calcd for CnHi₂F₂O₃S: C, 50.37; H, 4.61. Found: C, 50.41; H, 4.65.

(5)-(+-)-2-Amino-5,7-difluoro-1,2,3,4-tetrahydroanaphthalene hydrochloride. Sodium azide (40.0 g, 0.62 mol) was added to DMSO (1 L) with stirring until a clear solution was obtained. The mesylate (138 g, 0.53 mol) was added in one portion and the mixture
heated at 50° C for 16 h under a N₂ atmosphere. The reaction mixture was diluted with H₂O (1.8 L) and extracted with pentane (4 x 250 mL) followed by sequentially washing the combined pentane extracts with H₂O (2 x 100 mL), brine (100 mL) and drying over MgSO₄. Evaporation of the solvent under reduced pressure gave a volatile oil which was rapidly chromatographed on silica using pentane as the eluent to give dihydronaphthalene (8.50 g, 51.2 mmol) as a volatile oil. Further elution with pentane/CH₂Cl₂ (9:1) afforded the azide (101 g, 483 mmol) as a colorless oil: IR (CHCl₃) 2103 cm⁻¹; m/z 171 (M⁺). The azide 6a was dissolved in EtOAc (1200 mL) and hydrogenated over 10% Pd/C (6 g) in a 2.5 L Parr bottle (60 psi) for 6 h. After each hour, the bottle was evacuated and recharged with hydrogen to remove evolved N₂. The resulting mixture was filtered through Celite, stirred with ethereal HCl (IN, 500 mL), and the fine precipitate filtered off and washed with EtOAc, and then anhydrous ether. (The filtration took about 4 h). The moist solid was transferred to a round-bottom flask, and the remaining solvent removed in vacuo to give a white solid (90.4 g, 412 mmol; 77.9%): mp >280 0°C; [α]₂⁵⁰_D -60.2° (c =2.68, MeOH); ¹H NMR (d₆-DMSO) δ 1.79 (m, IH), 2.33 (m, IH), 2.63 (m, IH), 2.83-2.92 (m, 2H), 3.14 (dd, J = 16.7, 5.0 Hz, IH), 3.46 (m, IH), 6.93 (d, J = 9.4 Hz, IH), 7.00 (dt, J = 9.4, 2.5 Hz, IH). Anal. Calcd for C₁₀H₁₂ClF₂N : C, 54.68; H, 5.51; N, 6.37. Found: C, 54.31; H, 5.52; N, 6.44. The spectra for the (7R>enantiomer 8b are identical: mp >280 0°C; [α]₂⁵⁰_D +58.5° (c = 1.63, MeOH). Anal. Calcd for C₁₀H₁₂ClF₂N : C, 54.68; H, 5.51; N, 6.37. Found: C, 54.64; H, 5.51; N, 6.40.

[0105] (5)-(5-Difluoro-1,2,3,4-tetrahydronaphth-2-yl)(cyanomethyl)amine. The amine hydrochloride 8a (50.27 g, 229 mmol) was treated with a solution of NaOH (10.0 g, 250 mmol) in water (150 mL), followed by a few additional pellets of NaOH sufficient to obtain a solution. Further water (300 mL) was added and the mixture placed in a 50 °C bath and treated with formaldehyde sodium bisulfite complex (30.8 g, 230 mmol). After the mixture had been stirred for 30 min, KCN (15.0 g, 230 mmol) was added. The reaction mixture was stirred for a further 1 h at 80 °C, cooled to room temperature, and extracted with EtOAc to give an oil (51.3 g) which solidified. TLC (5% MeOH-CH₂Cl₂) showed ca. 10-15% of starting amine remained. Chromatography on silica gave the nitrile product (39.4 g) and starting free amine (7.12 g), which quickly forms the carbonate in air. Recycling this amine gave an additional 5.35 g of product. Combined yield (44.8 g, 202 mmol; 87.5%): mp 73.1-76.5 0°C; [α]₂⁵⁰_D -58.0° (c = 1.63, CHCl₃); ¹H NMR (CDCl₃) δ 1.50 (br s, IH), 1.70 (m, IH), 2.05 (m, IH), 2.55-3.04 (m, 4H), 3.22 (m, IH), 3.70 (s, 2H), 6.62 (m, 2H); MS m/z 222 (M⁺). Anal. Calcd for C₁₂H₁₂F₂N₂ : C, 64.85; H, 5.44; N, 12.60. Found: C, 65.07; H, 5.47; N,
12.44. The spectra for the (7?;enantiomer 9b are identical: mp 64.4-73.6 °C; [α]D25 +52.3° (c =2.12, CHCl3). Anal. Calcd for C12H12F2N2: C, 64.85; H, 5.44; N, 12.60. Found: C, 65.14; H, 5.54; N, 12.53.

(5)-(7-Difluoro-1,2,3,4-tetrahydronaphth-2-yl)-5-cyano-2,3-dihydro-2-thiox0-l H-imidazole. The nitrile (44.7 g, 201 mmol) in butyl formate (240 mL) was heated at reflux (120 °C bath) under N2 for 19 h, and the solvent then removed under reduced pressure. Toluene was added and evaporated to remove last traces of solvent, and the residue was dried under high vacuum to give an oil (53.2 g). The resulting formamide and ethyl formate (48.7 mL, 44.7 g, 604 mmol) in anhydrous THF (935 mL) were cooled in ice/MEOH (-15 °C) and stirred while J-BuOK (IM in THF, 302 mL, 302 mmol) was added over 20 min. After the reaction had been stirred for 18 h, the solvent was evaporated, the residue dissolved in IN HCl (990 mL) and ethanol (497 mL), and treated with KSCN (78.1 g, 804 mmol). The mixture was stirred for 135 min at 85 °C and then placed in an ice bath to give a precipitate. The filtered solid was loaded as a slurry in 10% MeOH/CH2Cl2 on to a silica (1 kg) column packed in hexane. Elution with 10% acetone/CH2Cl2 gave the product (18.05 g, 62.1 mmol; 30.8%): m.p. 240.7-249.2 °C; [V]D25 -69.1° (c =1.18, DMSO); 1H NMR (d6-DMSO) δ 2.18 (br m, IH), 2.47 (m, IH), 2.75 (m, IH), 3.03-3.35 (m, 3H), 5.19 (m, IH), 6.94 (d, J = 9.3 Hz, IH), 7.03 (dt, J = 9.3, 2.4 Hz, IH), 8.29 (s, IH), 13.3 (br s, IH); MS m/z 291 (M+). Anal. Calcd for C14H16F2N3S: C, 57.72; H, 3.80; N, 14.42. Found: C, 57.82; H, 3.92; N, 14.37.

(Further elution of the column with 1:1 MeOH/CH2Cl2 gave the primary amide 1a: mp 261.9-262.7 °C; [V]D25 -90.5° (c = 0.398); IR (KBr) 1593, 1630 cm⁻¹; 1H NMR (d6-DMSO) δ 2.14 (m, IH), 2.15-2.28 (m, IH), 2.74-3.05 (m, 4H), 5.64 (m, IH), 6.90 (d, J = 9.2 Hz, IH), 7.05 (dt, J = 9.5, 2.4 Hz, IH), 8.73 (s, IH), 9.70 (br s, IH), 13.7 (br s, IH); MS m/z 309 (M+). Anal. Calcd for C14H13F2N3OS•0.25H2O: C, 53.57; H, 4.33; N, 13.39. Found: C, 53.32; H, 3.96; N, 13.24. The spectra for the (7?;enantiomer are identical: mp 243.1-244.7 °C; [V]D25 +74.9° (c = 2.14, DMSO). Anal. Calcd for C14H16F2N3S: C, 57.72; H, 3.80; N, 14.42. Found: C, 57.85; H, 3.85; N, 14.45.

(5)-l-(5,7-Difluoro-1,2,3,4-tetrahydronaphth-2-yl)-5-aminomethyl-2,3-dihydro-2-thiox0-l H-imidazole. The above nitrile (5.00 g, 17.2 mmol) in THF (75 mL) was stirred under argon in an ice bath until a homogeneous solution was obtained. A solution of LAH in THF (1 M, 34.3 mL, 34.3 mmol) was added dropwise over 10 min, then the solution was stirred for 30 min at 0 °C and allowed to come to room temperature for 1.5 h. The reaction was again cooled to 0 °C and treated with a saturated solution of sodium potassium tartrate
until the mixture became freely stirable. Further tartrate solution (30 mL) was added, followed by 10% MeOH/CH₂Cl₂ (200 mL) and the mixture stirred for 15 min and treated with water (100-150 mL). The organic layer was separated and the aqueous phase extracted with 10% MeOH/CH₂Cl₂ (2 x 125 mL). The combined extracts were washed, dried (MgSO₄), and evaporated. Chromatography of the residue (5.2 g) on silica eluting with 5% MeOH/CH₂Cl₂ gave the free amine (2.92 g, 9.89 mmol; 58%): mp 170 °C; [α]D²³ = 11.0° (c = 1.59, DMSO). Anal. Calcd for C₁₄H₁₃F₁₂N₃SO₂.25H₂O: C, 56.07; H, 5.21; N, 14.01. Found: C, 56.11; H, 5.10; N, 14.14.

(5)-1-(5,7-Difluoro-1,2,3,4-tetrahydronaphth-2-yl)-5-aminomethyl-2,3-dihydro-2-thiooxo-1 H-imidazole hydrochloride (nepicatstat). The hydrochloride salt was prepared by the addition of ethereal HCl (1M, 20 mL, 20 mmol) to the free amine 2a (3.12 g, 10.6 mmol) which had been dissolved in MeOH (250 mL) by warming. The solvent was partially removed under reduced pressure and displaced by co-evaporation with EtOAc several times without evaporating to dryness. The resulting precipitate was treated with EtOAc (150 mL) and ether (150 mL), filtered off, washed with ether, and dried under nitrogen and then under high vacuum at 78 °C for 20 h to give the hydrochloride salt (3.87 g): mp 245 °C (dec); [α]D²⁵ = +9.65° (c = 1.70, DMSO); (93% ee by chiral HPLC); ¹H NMR (T = 320 °K, DMSO) δ 2.07 (m, 1H), 2.68-3.08 (m, 4H), 4.09 (m, 3H), 4.77 (m, 1H), 6.84 (m, 2H), 7.05 (s, 1H), 8.57 (br s, 3H), 12.4 (br s, 1H). Anal. Calcd for C₁₄H₁₆Cl₁₂F₂N₃S•0.5H₂O: C, 49.33; H, 5.03; N, 12.33. Found: C, 49.44; H, 4.96; N, 12.18. The spectra for the (7R)-enantiomer (R)-1-(5,7-Difluoro-1,2,3,4-tetrahydronaphth-2-yl)-5-aminomethyl-2,3-dihydro- are identical; mp 261-263 °C; [α]D²⁵-10.8° (c = 1.43, DMSO), 91.6% ee by chiral HPLC. Anal. Calcd for C₁₄H₁₆Cl₁₂F₂N₃S•0.3SH₂O: C, 49.73; H, 4.98; N, 12.42. Found: C, 49.80; H, 4.93; N, 12.39.

Nepicatstat was demonstrated to be a competitive inhibitor of bovine (IC₅₀ = 8.5 ± 0.8 nM) and human (IC₅₀ = 9.0 ± 0.8 nM) DBH. The i?-enantiomer (R)-1-(5,7-Difluoro-1,2,3,4-tetrahydronaphth-2-yl)-5-aminomethyl-2,3-dihydro- (IC₅₀ = 25.1 ± 0.6 nM; 18.3 ± 0.6 nM) and SKF 102698 (IC₅₀ = 67.0 ± 4.2 nM; 85.0 ± 3.7 nM) are less potent inhibitors of the bovine and human enzymes, respectively. DBH activity was assayed by measuring the conversion of tyramine to octopamine. Bovine DBH from adrenal glands was obtained from Sigma Chemical Co (St Louis, MO). Human secretory DBH was purified from the culture medium of the neuroblastoma cell line SK-N-SH. The assay was performed at pH 5.2 and 32 °C in 0.125 M NaOAc, 10 mM fumarate, 0.5 - 2 µM CUSO₄, 0.1 mg/mL catalase, 0.1 mM tyramine and 4 mM ascorbate. In a typical assay, 0.5 - 1 milliunits of enzyme were added to
the reaction mixture and then a substrate mixture containing catalase, tyramine and ascorbate was added to initiate the reaction (final volume of 200 µL). Samples were incubated with or without the appropriate concentration of the inhibitor at 37 °C for 30 - 40 min. The reaction was quenched by the stop solution containing 25 mM EDTA and 240 µM 3-hydroxytyramine (internal standard). The samples were analyzed for octopamine by reverse phase HPLC using UV detection at 280 nM. The remaining percent activity was calculated based on controls (without inhibitor), corrected using internal standards and fitted to a non-linear 4-parameter concentration-response curve to obtain IC50 values.

[0110] The activity of nepicastat at eleven different enzymes was determined using established assays. The affinity of nepicastat for thirteen selected receptors was determined by radioligand binding assays using standard filtration techniques and membrane preparations. Binding data were analyzed by iterative curve fitting to a four parameter logistic equation. K_i values were calculated using the Cheng-Prusoff equation. Figure 1 shows a table describing the interaction of nepicastat at DBH and a range of selected enzymes and receptors. Nepicastat showed weak affinity for a range of other enzymes and neurotransmitter receptors. These data suggest that nepicastat is a potent and highly selective inhibitor of DBH in vitro. Moreover, the S-enantiomer nepicastat is approximately 2-3 fold more potent than the R-enantiomer suggesting stereoselectivity.

[0111] Oral administration of nepicastat to spontaneously hypertensive rats (SHRs) and normal dogs produced potent and dose-dependent increases in tissue dopamine (DA)/norepinephrine (NE) ratios in peripheral arteries (renal or mesenteric), left ventricle and cerebral cortex. Chronic oral administration of nepicastat to normal dogs also produced sustained increases in the plasma DA/NE ratio. In conscious SHRs, acute oral administration of nepicastat produced dose-dependent and long-lasting (> 4 h) antihypertensive effects and also attenuation of the pressor responses to pre-ganglionic sympathetic nerve stimulation. Serum T3 and T4 levels were unaffected by a dose (6.2 mg/kg, po, b.i.d. for 10 days) which elevated the dopamine/norepinephrine ratio in the mesenteric artery. On the basis of its ability to potently modulate the sympathetic drive to cardiovascular tissues, nepicastat has been clinical evaluated for the treatment of congestive heart failure.

[0112] Congestive heart failure (CHF) is a leading cause of mortality in the United States. CHF is characterized by marked activation of the sympathetic nervous system (SNS) and renin-angiotensin system (RAS). The simultaneous activation of these two neurohormonal systems has been increasingly implicated in the perpetuation and progression of CHF.
Therapeutic interventions which block the effects of these neurohormonal systems are likely to favorably alter the natural history of CHF. Indeed, angiotensin-converting enzyme (ACE) inhibitors, which block formation of angiotensin II, have been shown to reduce morbidity and mortality in CHF patients. ACE inhibitors, however, have a limited indirect ability to attenuate the SNS. Inhibition of the SNS with β-adrenoceptor antagonists is a promising approach that is currently under clinical evaluation. An alternative strategy to directly modulate the SNS is inhibition of norepinephrine (NE) biosynthesis via inhibition of dopamine β-hydroxylase (DBH), the enzyme responsible for conversion of NE to dopamine (DA). Inhibition of DBH would be expected to reduce tissue levels of NE and elevate tissue levels of DA thereby increasing the tissue DA/NE ratio. This approach has potential advantages over β-adrenoceptor antagonists, such as reduced stimulation of α-adrenoceptors and elevated DA levels that can produce renal vasodilation, natriuresis and diminished aldosterone release. Previous DBH inhibitors, such as fusaric acid and SKF-102698, have drawbacks such as low potency and specificity that have precluded their clinical development in heart failure.

Nepicastat was used in in vivo biochemical studies to study the effects in spontaneously hypertensive rats (SHRs) and normal beagle dogs. On the day of the study, the animals were weighed and randomly assigned to receive either placebo (vehicle) or the appropriate dose of nepicastat. Each rat was dosed orally three times, 12 h apart, beginning in the morning. At 6 h after the third dose, the rats were anesthetized with halothane, decapitated, and the tissues (cerebral cortex, mesenteric artery and left ventricle) were rapidly harvested, weighed, placed in iced 0.4 M perchloric acid, frozen in liquid nitrogen and stored at -70°C until analysis. Tissue NE and DA concentrations were assayed by HPLC using electrochemical detection. Male beagle dogs (10 - 16 kg, Marshall Farms USA Inc, North Rose, NY) were used in the study. On the day of the study, dogs were randomly assigned to receive either placebo (empty capsule) or the appropriate dose of nepicastat. Each dog was dosed twice a day for 4.5 days. 6 h after the first dose on day 5, the dogs were euthanized with pentobarbital and the tissues (cerebral cortex, renal artery, left ventricle) harvested, weighed, placed in iced 0.4 M perchloric acid, frozen in liquid nitrogen and stored at -70 °C until analysis. Tissue NE and DA concentrations were assayed by HPLC using electrochemical detection.

Oral administration of nepicastat produced dose-dependent increases in DA/NE ratios in the artery (mesenteric or renal), left ventricle and cerebral cortex in SHRs and dogs.
At the highest dose tested (100 mg/kg in SHRs and 5 mg/kg in dogs) the maximal increases in DA/NE ratio were 14, 11 and 3.2 fold (in SHRs) and 95, 151 and 80 fold (in dogs) in the artery, left ventricle and cerebral cortex, respectively. When tested at 30 mg/kg in SHRs, SKF-102698 (1) increased the DA/NE ratio by 5.5-fold, 3.5-fold and 2.7-fold, whereas nepicastat, at the same dose, increased the ratio by 8.3, 7.5 and 1.5 fold in the mesenteric artery, left ventricle and cerebral cortex, respectively. Compound B at 30 mg/kg in SHRs, produced only 2.6, 3.5 and 1.1 fold increases in the DA/NE ratio in the mesenteric artery, left ventricle and cerebral cortex, respectively. These data suggest that nepicastat produces the expected biochemical effects in both SHRs and dogs but is more potent in the latter species. Furthermore, nepicastat is more potent than its Compound B and SKF-102698 (1) in SHRs.

The chronic effects of nepicastat (14.5 day treatment) on the plasma DA/NE ratio were investigated in normal dogs. Animals were randomized to receive, orally, either placebo (empty capsule) or nepicastat (2 mg/kg, b.i.d) for 14.5 days. Daily blood samples were drawn, 6 h after the first dose, for the measurement of plasma concentrations of DA and NE. The samples were collected in tubes containing heparin and glutathione, centrifuged at -4 °C and stored at -70 °C until analysis.

Oral administration of nepicastat (2 mg/kg; b.i.d) produced a significant increase in the DA/NE ratio that attained its peak effect at approximately 6-7 days and then plateaued to a new steady-state between 7-14 days.

The in vivo hemodynamic activity of nepicastat was further assessed in conscious, restrained SHRs, a model having high sympathetic drive to cardiovascular tissues. Hemodynamic study in SHRs. Male SHRs (15 - 16 week old) were used in the study. The animals were lightly anesthetized with ether and the left femoral artery and vein were catheterized for measurement of blood pressure and drug administration, respectively. The animals were placed in restrainers and allowed to recover for 30 - 40 min. After obtaining baseline measurements, the animals were treated, orally, with either vehicle or the appropriate dose of nepicastat and hemodynamic parameters were continuously recorded for 4 h. The animals were then anesthetized with pentobarbital, placed on a heating pad (37 °C) and ventilated with a Harvard rodent ventilator. After administration of atropine (1 mg/kg, iv) and tubocurarine (1 mg/kg, iv), the animals were pithed through the orbit of the eye with a stainless steel rod. The pithing rod was stimulated electrically with 1 ms pulses of 80V at different frequencies (0.15, 0.45, 1.5, 5, 15 Hz) to obtain frequency-pressor response curves.
Oral dosing of nepicastat resulted in a dose-dependent antihypertensive effect. The animals were placed in restrainers and allowed to recover for 30 - 40 minutes. After obtaining baseline measurements, the animals were treated, orally, with either vehicle or the appropriate dose of nepicastat and hemodynamic parameters were continuously recorded for 4 h. Nepicastat produced significant (p < 0.05) lowering of mean arterial pressure at all doses and time points, except at 0.3 mg/kg (180, 210 and 240 min) and 1 mg/kg (30, 210 and 240 min).

A maximal decrease in mean blood pressure of 53 ± 4 mmHg (33% reduction relative to vehicle control) was observed at the 10 mg/kg dose. The response was slow in onset, reaching its plateau in 3-4 h. The precise reason for the loss of anti-hypertensive efficacy at the highest dose (30 mg/kg) is unclear at present. Heart rate was not significantly affected except for a slight yet significant decrease at 10 and 30 mg/kg, (9.8 and 10.5 %, respectively). Following this study, the rats were pithed and the effects of nepicastat on the pressor response to pre-ganglionic nerve stimulation (PNS) of the spinal cord were evaluated 5 h after dosing. The frequency-pressor response curve was shifted significantly (p< 0.05) to the right in a dose-dependent manner (maximum shift of ~ 5 fold in the frequency-response curve). The heart rate response to PNS was not significantly affected. These data suggest that nepicastat inhibits the sympathetic drive to the vasculature and is the probable mechanism for its anti-hypertensive effect in SHRs.

Since the heterocyclic portion of nepicastat is structurally similar to methimazole, a known potent suppressor of mammalian thyroid function, the effects of nepicastat on thyroid function were evaluated at doses of 2.0 and 6.2 mg/kg, po, b.i.d in iodine-deficient Sprague-Dawley rats (n = 9-12) for 10 days. Methimazole (1 mg/kg, po, b.i.d.), used as a positive control, caused a significant reduction in serum levels OfT₃ (day 3, 31 %, p < 0.05; days 7 and 9, 42 % and 44 %, p < 0.01) and T₄ (days 3 and 7, 46 % and 58 %, p < 0.01) 4 h post-dose, whereas nepicastat showed no significant effects throughout the study (days 3, 7 and 9). Both doses of nepicastat significantly raised the DA/NE ratio in the mesenteric artery (p < 0.01 relative to vehicle controls) but not in the cortex 4 h after the final dose on day 10.

The findings of this study suggest that nepicastat is a potent, selective and orally active inhibitor of DBH. The compound is also devoid of significant behavioral effects in animal models and these findings will be the subject of a future publication. As compound nepicastat effectively modulates the sympathetic drive to cardiovascular tissues, it has been tested for the treatment of CHF.
EXAMPLE 2

[0123] Bovine and human dopamine β-hydroxylase activity were assayed by measuring the conversion of tyramine to octopamine. Bovine adrenal dopamine β-hydroxylase was obtained from Sigma Chemicals (St Louis, MO, USA) whereas human dopamine β-hydroxylase was purified from the culture medium of the neuroblastoma cell line SK-N-SH. The assay was performed at pH 5.2 and 32°C in a medium containing 0.125 M NaAc, 10 mM fumarate, 0.5 - 2 µM CuSO4, 0.1 mg.ml⁻¹ catalase, 0.1 mM tyramine and 4 mM ascorbate. In a typical assay, 0.5 - 1 milliunits of enzyme were added to the reaction mixture and, subsequently, a substrate mixture containing catalase, tyramine and ascorbate was added to initiate the reaction (final volume of 200 µl). Samples were incubated with or without the appropriate concentration of nepicastat or Compound B at 37°C for 30 to 40 minutes. The reaction was quenched by the stop solution containing 25 mM EDTA and 240 µM 3-hydroxytyramine (internal standard). The samples were analyzed for octopamine by reverse phase high pressure liquid chromatography (HPLC) using ultraviolet-detection at 280 nm. The HPLC chromatography run was carried out at the flow rate of 1 ml.min⁻¹ using a LiChroCART 125-4 RP-18 column and isocratic elution with 10 mM acidic acid, 10 mM 1-heptane sulfonic acid, 12 mM tetrabutyl ammonium phosphate and 10% methanol. The remaining percent activity was calculated based on controls, corrected using internal standards and fitted to a non-linear four-parameter concentration-response curve.

[0124] Nepicastat (S-enantiomer) and Compound B (R-enantiomer) produced concentration-dependent inhibition of bovine and human dopamine β-hydroxylase activity. The calculated IC₅₀'s for nepicastat were 8.5 ± 0.8 nM and 9.0 ± 0.8 nM for the bovine and human enzyme, respectively. Compound B was slightly less potent (IC₅₀'S of 25.1 ± 0.6 nM and 18.3 ± 0.6 nM for the bovine and human enzyme, respectively) than nepicastat. Nepicastat was shown to be a potent inhibitor of human and bovine dopamine β-hydroxylase in vitro. The inhibitory effects of the compound were stereospecific since the S-enantiomer (nepicastat) was marginally, but significantly, more potent than the R-enantiomer (Compound B).

[0125] The activity of nepicastat at twelve selected enzymes and receptors was determined using established assays. A brief account of the principle underlying each of the enzymatic assays is given in Figure 2. Binding data were analyzed by iterative curve-fitting to a four parameter logistic equation. Ki values were calculated from IC₅₀ values using the
Cheng-Prusoff equation. Enzyme inhibitory activity was expressed as IC50 (concentration required to produce 50% inhibition of enzyme activity).

[0126] Nepicastat had negligible affinity (IC50s or Kis > 10 µM) for a range of other enzymes (tyrosine hydroxylase, acetyl CoA synthetase, acyl CoA-cholesterol acyl transferase, Ca2+/calmodulin protein kinase II, cyclooxygenase-I, HMG-CoA reductase, neutral endopeptidase, nitric oxide synthase, phosphodiesterase III, phospholipase A2, and protein kinase C) and neurotransmitter receptors (α1A, α1B, α2A, α2B, β1 and β2 adrenoceptors, M1 muscarinic receptors, D1 and D2 dopamine receptors, µ opioid receptors, 5-HT1A, 5-HT2A, and 5-HT2C serotonin receptors). Nepicastat displayed a high degree of selectivity for dopamine β-hydroxylase as the compound possessed negligible affinity for twelve other enzymes and thirteen neurotransmitter receptors.

[0127] In studies involving SHRs, the drugs, nepicastat ((S)-5-aminomethyl-l-(5,7-difluoro-l,2,3,4-tetrahydrophth-2-yl)-l,3-dihydroimidazole-2-thione hydrochloride) and the corresponding R-enantiomer (Compound B), were dissolved in distilled water and dosed orally with a gavage needle. In the dog studies, the drugs were filled in capsules and dosed orally. All doses are expressed as free base equivalents.

[0128] Male SHRs (15 - 16 weeks old, Charles River, Wilmington, MA, USA) were used in in vivo studies. On the day of the study, animals were weighed and randomly assigned to be dosed with either vehicle (control) or the appropriate dose of nepicastat (3, 10, 30 or 100 mg.kg⁻¹, po) or Compound B (30 mg.kg⁻¹, po) three consecutive times, twelve hours apart. At six hours after the third dose, the rats were anaesthetized with halothane, decapitated and tissues (cerebral cortex, mesenteric artery and left ventricle) were rapidly harvested, weighed, placed in iced perchloric acid (0.4 M), frozen in liquid nitrogen and stored at -70°C until subsequent analysis. To quantify noradrenaline and dopamine concentrations, tissues were homogenized by brief sonication and centrifuged at 13,000 rpm for 30 minutes at 4°C. The supernatant, spiked with 3, 4-dihydroxybenzyl amine (internal standard), was assayed for noradrenaline and dopamine by HPLC using electrochemical detection.

[0129] Basal tissue catecholamine content (µg.g⁻¹ wet weight) in control animals were as follows: mesenteric artery (noradrenaline, 10.40 ± 1.03; dopamine, 0.25 ± 0.02), left ventricle (noradrenaline, 1.30 ± 0.06; dopamine, 0.02 ± 0.00) and cerebral cortex (noradrenaline, 0.76 ± 0.03; dopamine, 0.14 ± 0.01). Nepicastat produced dose-dependent
reduction in noradrenaline content and enhancement of dopamine content and dopamine/noradrenaline ratio in the three tissues which were studied.

[0130] These changes attained statistical significance (p < 0.05) at doses of ≥ 3 mg.kg⁻¹ in the mesenteric artery and left ventricle but only at doses of 30 and 100 mg.kg⁻¹ in the cerebral cortex. At the highest dose studied (100 mg.kg⁻¹, po), the decreases in noradrenaline were 47%, 35%, 42% and increases in dopamine were 820%, 800% and 86% in the mesenteric artery, left ventricle and cerebral cortex, respectively. When tested at 30 mg.kg⁻¹, po, nepicastat produced significantly greater changes in catecholamine content, as compared to the R-enantiomer (Compound B), in the mesenteric artery and left ventricle.

[0131] Male beagle dogs (10 - 16 kg, Marshall Farms USA Inc, North Rose, NY, USA) were also used in in vivo studies. On the day of the study, dogs were weighed and randomly assigned to be orally dosed with either empty capsules (control) or the appropriate dose of nepicastat (0.05, 0.5, 1.5 or 5 mg.kg⁻¹; po, b.i.d.) for 5 days. At six hours following the first dose on day-5, the dogs were euthanized with pentobarbital and the tissues (cerebral cortex, renal artery, left ventricle) were rapidly harvested. The tissues were subsequently processed and analyzed for noradrenaline and dopamine.

[0132] Data are expressed as mean ± standard error of the mean (SEM). Tissue and plasma catecholamine data were analyzed using a non-parametric one-way analysis of variance (ANOVA) or two-way ANOVA, respectively, followed by pairwise comparison using Fisher LSD test. P < 0.05 was considered statistically significant.

[0133] Basal tissue catecholamine content (µg.g⁻¹ wet weight) in control animals were as follows: renal artery (noradrenaline, 10.7 ± 1.05; dopamine, 0.22 ± 0.01), left ventricle (noradrenaline, 2.11 ± 0.18; dopamine, 0.07 ± 0.03) and cerebral cortex (noradrenaline, 0.26 ± 0.02; dopamine, 0.03 ± 0.00). When compared to control animals, nepicastat produced a dose-dependent reduction in noradrenaline content and enhancement of dopamine content and dopamine/noradrenaline ratio in the three tissues which were studied.

[0134] These changes attained statistical significance (p < 0.05) at doses of ≥ 0.1 mg.kg⁻¹.day⁻¹ in the three tissues. At the highest dose studied (5 mg.kg⁻¹, b.i.d., po), the decreases in noradrenaline were 88%, 91% and 96% and increases in dopamine were 627%, 700% and 166% in the renal artery, left ventricle and cerebral cortex, respectively.

[0135] Male beagle dogs were randomized to be orally dosed with either empty capsules (control) or nepicastat (2 mg.kg⁻¹, po, b.i.d.) for 15 days. Daily venous blood samples were
drawn, six hours after the first dose, for measurement of plasma concentrations of dopamine and noradrenaline. The samples were collected in tubes containing heparin and glutathione, centrifuged at -4°C and the separated plasma was stored at -70°C until analysis. The baseline concentrations of catecholamines in two groups of animals were not significantly different from each other: plasma noradrenaline and dopamine concentrations were 460.3 ± 59.6 and 34.4 ± 11.9 pg.ml⁻¹, respectively, in the control group and 401.9 ± 25.5 and 41.1 ± 8.8 pg.ml⁻¹, respectively, in the nepicastat-treated group. When compared to the control group, nepicastat (2 mg.kg⁻¹, b.i.d, po) produced significant decreases in plasma concentrations of noradrenaline and increases in plasma concentrations of dopamine and dopamine/noradrenaline ratio.

[0136] Inhibitory modulation of sympathetic nerve function, through pharmacological means, is an attractive therapeutic strategy for the management of congestive heart failure, inasmuch as elevated activity of this system has been implicated in the progressive worsening of the disease. The aim of this study was to pharmacologically characterize the effects of nepicastat, a compound which modulates noradrenaline synthesis in sympathetic nerves by inhibiting the enzyme dopamine β-hydroxylase.

[0137] Inhibition of dopamine β-hydroxylase *in vivo* would be expected to result in elevated levels of the substrate (dopamine) and diminished levels of the product (noradrenaline) in tissues which receive noradrenergic innervation. This expectation was borne out in experiments which investigated the effects of nepicastat on catecholamine levels in central and peripheral tissues *in vivo*. In both SHRs and beagle dogs, nepicastat produced dose-dependent reductions in noradrenaline content and increases in dopamine content in peripheral (mesenteric or renal artery, left ventricle) and central (cerebral cortex) tissues. In this respect, Compound B was less potent than nepicastat which is consistent with the lower IC₅₀ of the former enantiomer for the enzyme. Although dopamine/noradrenaline ratio was also elevated, there did not appear to be stoichiometric replacement of noradrenaline with dopamine. The most likely explanation for this finding is that tissue levels of dopamine may have been underestimated due to intraneuronal metabolism of dopamine.

[0138] The ability of nepicastat to alter catecholamine levels in the cerebral cortex suggests that the drug does penetrate the blood brain barrier. In dogs, the magnitude of the changes in catecholamines in the cerebral cortex appeared comparable to those in peripheral tissues. In SHRs, however, nepicastat, at low doses (< 10 mg.kg⁻¹), produced significant changes in noradrenaline and dopamine content in peripheral tissues without affecting
catecholamines in the cerebral cortex. This suggests that, at least in SHRs, the drug does possess modest peripheral selectivity.

[0139] Plasma noradrenaline concentrations provide a useful measure of overall sympathetic nerve activity although this parameter may be influenced by alterations in neuronal uptake and metabolic clearance of the catecholamine. Baseline concentrations of noradrenaline in the plasma were surprisingly elevated in the dogs, which perhaps, is a reflection of the initial stress induced by the phlebotomy blood-sampling procedure. Nevertheless, compared to the control group, nepiclastat produced significant decreases in plasma noradrenaline concentrations consistent with reduced transmitter synthesis and release although an indirect effect, secondary to facilitation of neuronal uptake or metabolic clearance, cannot be discounted. Since released noradrenaline represents a small fraction of the total neuronal noradrenaline stores, an inhibitor of noradrenaline biosynthesis would affect noradrenaline release only after existing stores of the catecholamine have been sufficiently depleted. Accordingly, the decreases in plasma noradrenaline concentrations did not attain statistical significance until 4 days of dosing with nepiclastat suggesting gradual modulation of the sympathetic nervous system.

[0140] A growing body of evidence suggests that chronic activation of the sympathetic nervous system in congestive heart failure is a maladaptive response. This contention is supported by clinical trials which have shown a beneficial effect of carvedilol in congestive heart failure patients with respect to long-term morbidity and mortality. However, it should be noted that most patients do require some level of sympathetic drive to support cardiovascular homeostasis. Indeed, the therapeutic value of β-blockers, including carvedilol, may be limited by their propensity to cause hemodynamic deterioration especially during initiation of therapy. This unwanted effect, which results from abrupt withdrawal of sympathetic support, necessitates careful dose-titration. Inhibitors of dopamine β-hydroxylase, such as nepiclastat, may be devoid of this undesirable effect for the following reasons. First, this class of drugs would attenuate, but not abolish, noradrenaline release and, second, they produce gradual modulation of the system thereby obviating the need for dose-titration. Another advantage of nepiclastat over β-blockers is that it enhances dopamine levels which, via agonism of dopamine receptors, may have salutary effects on renal function such as renal vasodilation, diuresis and natriuresis.
Nepicastat is a potent, selective and orally active inhibitor of dopamine β-hydroxylase which may be of value in the treatment of cardiovascular disorders associated with over-activation of the sympathetic nervous system.

EXAMPLE 3

Following oral administration of [14C]-nepicastat, the majority of the radioactivity in plasma was associated with nepicastat, an N-linked glucuronide of nepicastat (Metabolite 2, M2), and an unidentified polar fraction (M1). There was no significant accumulation of nepicastat with multiple dosing and T1/2 was similar after single and multiple doses. T1/2 was 10 -14 hours. No significant differences in the Cmax or AUC for nepicastat were noted between subjects with the fast acetylator phenotype and those with the slow acetylator phenotype, although Cmax and AUC for the N-acetyl metabolite were, as expected, much lower in the slow acetylators than in the fast acetylators. In a study comparing the pharmacokinetics of a 40 mg tablet taken while fasting or after a meal, there was no significant difference in the plasma concentrations. T1/2 was increased to 3.5 hours after a meal from 1.4 hours in the fasted state.

The pharmacokinetics of nepicastat after a single 40 mg dose was compared in men and women. The AUC in women was approximately 43% greater than in men and the Cmax approximately 23% greater in women than in men. The T1/2 was longer in women than in men. Comparing the pharmacokinetics of nepicastat following 10 days of dosing with a 40 mg dose, the AUC was higher in healthy subjects than in patients with CHEF, with no difference in the T1/2. There was no significant accumulation with multiple dosing in either population.

In humans, compound-related radioactivity is rapidly eliminated. On average, 87.4% of the administered radiolabel was recovered in the first 72 hours with 82.4% in the urine and 5.01% in the feces. After 10 days, the mean total recovery of the radiolabel was 93.8%. In plasma, the Tax, for the radioactivity was 1-2 hours (similar to that for nepicastat). In both rapid and slow acetylators, an N-linked glucuronide of nepicastat accounted for the greatest percentage of the total radioactivity in plasma (26.8%) and urine (57.9%) over 0 to 48 hours. The terminal T1/2 for total radioactivity in plasma was found to be very long (-100 hours), most likely due to a polar fraction present in low concentrations that was slowly eliminated.
EXAMPLE 4

[0145] In a study designed to assess the effects of nepicastat on cognitive function, subjects treated with 5 or 40 mg of nepicastat demonstrated no significant impairment of mood, sleep, or cognition. In studies of thyroid uptake of $^{123}$I, doses of 5, 40, and 100 mg of nepicastat demonstrated no differences from placebo. Reduction of uptake after a single 200 mg dose of nepicastat was significantly greater than placebo, but significantly less than that following a 10 mg dose of methimazole. In single-dose Phase I studies, doses from 5 to 800 mg (dose calculation based on the hydrochloride salt) of nepicastat were generally well tolerated in healthy men.

EXAMPLE 5

[0146] In a multiple-dose Phase I study of nepicastat, doses of 5 and 40 mg were generally well tolerated in healthy men.

[0147] Five of the 6 subjects treated for 8 days or longer with 200 mg developed a rash which resolved spontaneously.

[0148] One subject developed atrial arrhythmias and intermittent right bundle branch block after 6 days of dosing with 200 mg of nepicastat.

EXAMPLE 6

[0149] Sixteen non-treatment-seeking cocaine-dependent volunteers are studied as inpatients using a double-blind, placebo-controlled, within-subjects design. After giving informed consent, potential volunteers complete outpatient psychiatric and medical screening. Eligible volunteers are admitted and a physical examination, EKG, pregnancy testing and psychiatric testing are completed. The study utilizes a dose-escalation design in which participants (n=12) receive ascending doses of cocaine (0 mg, 10 mg, 20 mg, and 40 mg) during daily treatment with ascending doses of nepicastat (0 mg, 80 mg, 160 mg). A parallel group of participants (n=4) receive only daily treatment with placebo for the duration of the study in order to maintain the blind. Treatment at each dose level are daily for 4 days, or well over 4 half-lives of nepicastat, which is 10 to 14 hours. On the 4th day of treatment at each dose level, participants receive cocaine 0 mg, 10 mg, 20 mg, and 40 mg in that order. Cocaine is administered at hourly intervals, providing sufficient time for both the cardiovascular and subjective effects to return to baseline.
Cardiovascular indices are carefully monitored using continuous EKG and frequent blood pressure during all procedures involving the administration of cocaine, and stopping parameters are in place so that cocaine is not be administered if cardiovascular indices exceed preset limits. Previous studies have shown that 6 doses of 32 mg cocaine given at 14-minute intervals is safe, and extending the inter-dose interval to 1 hour may enhance safety further. Blood samples are collected for analysis of the pharmacokinetics of 10 mg cocaine administered on the 3rd day of treatment with 0 mg nepicastat and again on the 3rd day of treatment with 80 mg and 160 mg nepicastat. The effects of nepicastat on the pharmacokinetics of cocaine are studied. Based on existing information, no interaction is expected.

About 12 days are required for each participant to complete the study. The 16 participants may complete the study within one year.

In order to participate in the study, participants must have:

1. Been English-speaking volunteers who were not seeking treatment at the time of the study;
2. Been between 18-55 years of age;
3. Met DSM-IV TR criteria for cocaine dependence;
4. Had a self-reported history of using cocaine by the IV route and provided at least one cocaine-positive urine prior to admission;
5. Had vital signs as follows: resting pulse between 50 and 95 bpm, blood pressures between 85-150 mm Hg systolic and 45-96 mm Hg diastolic; this criterion must have been met within 2 days of admission;
6. Had hematology and chemistry laboratory tests that were within normal (+/-10%) limits with the following exceptions: a) liver function tests (total bilirubin, ALT, AST, and alkaline phosphatase) \( \leq 3 \times \) the upper limit of normal, and b) kidney function tests (creatinine and BUN) \( \leq 2 \times \) the upper limit of normal;
7. Had a baseline EKG that demonstrates clinically normal sinus rhythm, clinically normal conduction, and no clinically significant arrhythmias;
8. Had a medical history and brief physical examination demonstrating no clinically significant contraindications for study participation, in the judgment of the admitting physician and the principal investigator.

[0153] Potential participants were excluded from participation in the study if any of the following applied:

1. Any history or evidence suggestive of seizure disorder or brain injury;

2. Any previous medically adverse reaction to cocaine, including loss of consciousness, chest pain, or epileptic seizure;

3. Neurological or psychiatric disorders, such as: (a) psychosis, bipolar illness or major depression as assessed by SCID; (b) organic brain disease or dementia assessed by clinical interview; (c) history of any psychiatric disorder which would require ongoing treatment or which would make study compliance difficult; (d) history of suicide attempts within the past three months assessed by SCID and/or current suicidal ideation/plan as assessed by SCID;

4. Evidence of clinically significant heart disease or hypertension, as determined by the PI, though participants may be taking antihypertensive medication;

5. A family history in first-degree relatives of early cardiovascular morbidity or mortality, as determined by the PI;

6. Evidence of untreated or unstable medical illness including: neuroendocrine, autoimmune, renal, hepatic, or active infectious disease;

7. Had HIV and were currently symptomatic, had a diagnosis of AIDS, or were receiving antiretroviral medication;

8. Were pregnant or nursing. Other females must either have been unable to conceive (i.e., surgically sterilized, sterile, or post-menopausal) or have been using a reliable form of contraception (e.g., abstinence, birth control pills, intrauterine device, condoms, or spermicide). All females were required to provide negative pregnancy urine tests before study entry, upon hospital admission, and at the end of study participation;

9. Had asthma or were currently using alpha or beta agonists, theophylline, or other sympathomimetics;
10. Had any other illness, condition, or use of psychotropic medications, which in the opinion of the PI and/or the admitting physician would have precluded safe and/or successful completion of the study.

Criteria for Discontinuation Following Initiation

1. Positive urine drug screen or breath test indicating illicit use of cocaine, cocaine, alcohol, opiates, or other abused drugs not delivered as part of this protocol;
2. Inability to comply with study procedures;
3. Meet discontinuation criteria due to exaggerated response to cocaine, described below.

Stopping Criteria

[0154] Participants were required to continue to meet inclusion criteria in order to remain in the protocol. Cocaine administration was not initiated if there were clinically significant arrhythmias or if vital signs are outside of acceptable ranges: resting pulse < 130 bpm and blood pressure below 165 mm Hg systolic and 100 mm Hg diastolic. These values are higher than those of the inclusion/exclusion criteria because transient increases in vital signs can occur in expectation of receiving cocaine. In addition, repeated doses of cocaine were not administered (and the study physician halted continued cocaine delivery) if there were behavioral manifestations of cocaine toxicity (agitation, psychosis, inability to cooperate with study procedures).

Stopping Criteria for Further Participation

[0155] Subject participation was terminated if any of the following events occurred:
1. Systolic BP > 180 mm Hg sustained for 5 minutes or more;
2. Diastolic BP > 120 mm Hg sustained for 5 minutes or more;
3. Heart rate > (220 - age x 0.85) bpm sustained for 5 minutes or more.

Rationale for Subject Selection Criteria

[0156] Participants were required to have used cocaine by the IV route to avoid exposing participants to routes of administration that produce more intensive interoceptive effects. The age criteria were selected primarily to avoid enrolling participants with undiagnosed cardiovascular disease. Participants with active HIV disease were excluded to avoid potential
exacerbation of their underlying disease; participants with asymptomatic HIV were included because this group is at high risk for cocaine dependence. Participants with asthma (or who take asthma medications) were excluded due to potential adverse interactions between beta agonist medications and cocaine.

Study Medications

[0157] Cocaine produces prototypical stimulant effects by inhibiting the uptake of DA, NE, and serotonin into presynaptic storage granules. Cocaine has a short elimination half-life, about 90 min. The principal clinical effects of cocaine are psychomotor activation and increases in sympathetic tone, evident as increases in heart rate and blood pressure.

[0158] Cocaine is administered at up to 40 mg in single doses and up to 200 mg in self-administration sessions consisting of 10 doses of 20 mg administered at 13 min intervals. These doses are modest compared to amounts that participants in these studies have reported using daily; typical daily dosing patterns are on average 250 mg to 500 mg or more.

[0159] Doses much higher than those proposed here have been associated with seizures and with severe cardiovascular toxicity and death. These potential toxicities are ameliorated by the use of relatively low doses, careful screening of potential volunteers, by careful monitoring of participants following administration of cocaine, and by the ready availability of medical intervention in the case of an adverse event.

[0160] Cocaine is administered IV, so availability is complete. Cocaine is metabolized primarily to benzoylecgonine by plasma esterases that are not known to be affected by nepicastat. Benzoylecgonine and other minor metabolites are excreted renally.

[0161] Cocaine for IV use in humans is obtained from a NIDA contractor and a letter of authorization to allow us to reference NIDA’s IND for cocaine is obtained and submitted to the FDA.

[0162] Ascending doses of nepicastat (0 mg, 80 mg, and 160 mg) are administered at 7 AM. Treatment at each dose level is continued for 4 days.

[0163] By starting at a lower dose and increasing the dose after completing the first series of study procedures, the risks of the combination of nepicastat and cocaine are be minimized. This approach also may reduce the risk for rash, which occurred in 7% to 20% of volunteers thus far. Rash incidence was associated with dose and treatment duration. Doses above 160 mg conferred a greater risk for rash.
[0164] No pharmacokinetic interactions are expected because nepicastat is not an enzyme inhibitor, though pharmacokinetic assessment of the 10 mg dose of cocaine administered on the 3rd day of treatment at each dose level of nepicastat can confirm this. Because nepicastat reduces the synthesis of NE, the rewarding effects of cocaine may be lower during treatment with nepicastat. Because nepicastat increases plasma and brain concentrations of DA, DA-mediated side effects such as paranoia may occur. These symptoms were not observed during the trials for CHF, but stimulants were not administered in those studies.

[0165] Following consent, participants are required to submit a cocaine-positive urine sample for documentation of ongoing drug use. Some participants (limited by the number of devices available) are also asked to wear a telemetry device during screening and throughout the study that records heart rate and movement. Data from this device can identify drug use episodes based on changes in these parameters.

[0166] To control nicotine exposure, smoking is prohibited within 2 hours of study procedures involving cocaine administration or cue exposure. Participants are required to refrain from illicit and prescription drug use for the duration of the study and this is confirmed with daily urine and breath alcohol level testing.

[0167] Experimental sessions are conducted at approximately the same time of day for a given participant. Cocaine is administered in an experimental room. Cocaine is administered using a syringe pump, which administers the correct dose of cocaine or saline placebo over 2 minutes. During and for 1 hour after drug administration sessions heart rate and blood pressure are monitored.

[0168] Participants undergo a targeted history and physical examination. Blood is drawn for standard laboratory examination, including CBC, electrolytes, LFT, and creatinine. HIV screening is performed as a service to participants and those testing positive are counseled and referred for treatment.

[0169] The Actiheart MiniMitter is used to measure heart rate and movement prior to admission in some volunteers (the number is limited by the number of devices available). The MiniMitter attaches to the participants' skin using paste and non-invasively records EKG and movement for up to two weeks. The data can be downloaded to a PC for analysis later.

[0170] Participants must meet DSM-IV-TR criteria for cocaine and nicotine dependence, determined by the Mini International Neuropsychiatric Interview (MINI) and defined by inclusion/exclusion criteria. The MINI is a short, structured diagnostic interview developed
in 1990 by psychiatrists and clinicians in the United States and Europe for DSM-IV TR and ICD-IO psychiatric disorders. The MINI is the structured psychiatric interview of choice for psychiatric evaluation and outcome tracking in clinical psychopharmacology trials and epidemiological studies, and is the most widely used psychiatric structured diagnostic interview instrument in the world. This instrument can be used to determine whether the subject met DSM-IV TR criteria for drug dependence and to rule out any major psychiatric disorders (e.g., affective disorders, schizophrenia).

[0171] The Addiction Severity Index-Lite Clinical Factors (ASI-Lite CF) version is administered by a trained research staff member during screening. The ASI-Lite is the interviewer's estimate of the severity of the participant's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores. The family history section of the ASI, as the ASI-Lite version collects minimal family history information, are retained.

[0172] There is a third-generation Beck Depression Inventory (BDI), revised in 1996. The instrument retains its original 21-item questionnaire format that requires approximately 10 minutes to complete. The BDI-II has been validated against the BDI-IA and continues to be an excellent index of depression/distress. This indicator is used to monitor participants who become clinically depressed during the trial, making it also a measure for participants' safety.

[0173] Current attention deficit hyperactivity disorder (ADHD) symptoms are assessed weekly, using the ADHD-IV rating scale.

[0174] The apathy scale from the Neuropsychiatric Inventory are collected at baseline.

[0175] DNA is collected with buccal swabs applied to Whatman FTA cards. These cards allow safe and stable storage of biological samples for DNA extraction. The anticipated yield of genomic DNA is 50-100 μg, which is adequate for over 500 genotype assays using currently available methods.

[0176] Genotypes are determined using 5' Exonuclease-based (Taqman) genotyping assays. Assays are developed by Applied Biosystems (ABI; Assays by Design). Allele discrimination are performed using the ABI 3730 realtime PCR cycler.

[0177] Blood samples for analysis of the pharmacokinetics of cocaine are collected during treatment with 0 mg nepicastat (study day 1) and during treatment with 80 mg and 160
mg nepicastat (study days 4 and 8). Blood samples are collected at -15, 20, 30, 40, 50, 60, 90, 120, 180, 240, 300, 360, 420 and 480 minutes following dosing of 10 mg cocaine on the 3\textsuperscript{rd} day of treatment with each dose level of nepicastat. Note that other doses of cocaine (0-40 mg) are administered on the 4\textsuperscript{th} day of treatment with each dose level of nepicastat, so the pharmacokinetic assessment does not interfere with the other assessments. Blood is collected and plasma separated and frozen at -70°C until analyzed. Cocaine and BE are assayed using liquid chromatography/tandem mass spectrometry (LC/MS/MS). The reference lab has a limit of quantification of 2.5 ng/ml for these assays. The pharmacokinetic analysis clarifies effects of nepicastat on the pharmacokinetics of cocaine.

[0178] DBH is stored in NE storage granules and is released along with NE. Plasma DBH thus gives a good index of enzymatic activity within the CNS. Blood is sampled daily at 10 AM (prior to cocaine/placebo dosing) and stored for subsequent analysis. DBH activity is measured by using the tyramine-octopamine method using a high performance liquid chromatographic-fluorometric system, as described previously. This allows examination of changes in DBH over time, providing an insight into the pharmacodynamics of nepicastat’s inhibition of DBH. The BDI is administered repeatedly throughout the protocol to monitor changes in mood.

[0179] Subjective effects are measured using a computerized visual analogue scale (VAS) consisting of a continuous 10 cm line digitized for scoring purposes from 0 to 100. Participants are required to move the cursor from off the left-hand extreme and onto the line by depressing the left or right mouse buttons for left and right movements on the line. The VAS is designed to provide rapidly acquired ratings of cocaine euphoria, dysphoria and craving. These include ratings of "Any Drug Effect," "High," "Good Effects," "Stimulated," and "Bad Effects," "Feel Paranoid," "Feel Suspicious," and "Would Use Cocaine if Available," "Crave Cocaine," "Could Refuse Cocaine Now," and "Desire Cocaine." VAS measures are collected prior to cocaine administration and at 5, 10, 15, 20, 30, and 45 minutes following drug administration.

[0180] Fifteen minutes after cocaine administration participants are asked how much they would pay for that dose of drug, based on $50/gm (current cost if purchases from illicit sources). This anchor is provided to standardize responses given that the price of cocaine varies over time and place.
On Day 13, the last day of treatment with study medication, all patients participate in the "Experimental Sessions" where subjects make a series of choices between money and a double blinded infusion of placebo (saline) or 20 mg cocaine. In one of the sessions, only placebo (saline) is available. In the other session, only 20 mg cocaine is available. Participants choose to either self-administer placebo or accept money and 20 mg cocaine vs. money. This occurs in the morning (am) and in the afternoon (pm), with the order randomized and counterbalanced so that placebo or nepicastat is administered first to equal numbers of subjects.

**Experimental (choice) session:**

During each session subjects are asked to make a series of choices between an infusion corresponding to a color ("blue" or "green"), and money. The color corresponds to the dose (cocaine 0 mg or 20 mg) administered to the subject during the sample session. For each of the 2 choice sessions, participants make 10 choices for the infusion (cocaine 0 mg IV in one session and cocaine 20 mg in the other) or money. The participant makes a series of choices between ascending value money options ($0.05, $0.05, $0.05, $0.05, $1, $4, $7, $10, $13, and $16) or cocaine (0 mg or 20 mg/IV/infusion) using a patient-controlled analgesia (PCA) pump.

Infusion choices are performed by the participant using the PCA button, while choices for money are indicated verbally to the investigator. Infusions take place over 2-min followed by a 3-min time-out period. As such, selections are made at 5-min intervals.

Participants receive cocaine doses immediately after indicating their choice, providing vital signs remain within preset limits up to a maximum of 200 mg cocaine (10 X 20 mg). Money choices are given directly to the patient immediately after the choice, but this money must be spent prior to discharge.

The table shows the Experimental choice sessions with 16 total participants.

<table>
<thead>
<tr>
<th>Choices</th>
<th>8 participants</th>
<th>8 participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>am Choice 1</td>
<td>0 mg cocaine IV or $0.05</td>
<td>20 mg cocaine IV or $0.05</td>
</tr>
<tr>
<td>am Choice 2</td>
<td>0 mg cocaine IV or $0.05</td>
<td>20 mg cocaine IV or $0.05</td>
</tr>
<tr>
<td>am Choice 3</td>
<td>0 mg cocaine IV or $0.05</td>
<td>20 mg cocaine IV or $0.05</td>
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<tr>
<td>Choices</td>
<td>8 participants</td>
<td>8 participants</td>
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<tr>
<td>am</td>
<td>Choice 4</td>
<td>0 mg cocaine IV or $0.05</td>
</tr>
<tr>
<td>am</td>
<td>Choice 5</td>
<td>0 mg cocaine IV or $1.00</td>
</tr>
<tr>
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<tr>
<td>am</td>
<td>Choice 10</td>
<td>0 mg cocaine IV or $16.00</td>
</tr>
<tr>
<td>pm</td>
<td>Choice 1</td>
<td>20 mg cocaine IV or $0.05</td>
</tr>
<tr>
<td>pm</td>
<td>Choice 2</td>
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<tr>
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<td>Choice 3</td>
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<td>Choice 9</td>
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<tr>
<td>pm</td>
<td>Choice 10</td>
<td>20 mg cocaine IV or $16.00</td>
</tr>
</tbody>
</table>

A sample size of 12 in the nepicastat-treated group allows detection of medium to large effects, which is appropriate for an initial assessment. The plot (Figure 3) shows the effect size achieved with sample sizes ranging from 5 to 15. Increasing the sample size above 12 would enhance analytical power to detect differences between the treatments but at increasing cost. The placebo-treated group is included only to maintain the blind and is not intended to serve as a comparison group.

The analysis focuses primarily on the effects of nepicastat in the nepicastat-treated group. The placebo-treated group is included primarily to maintain the blind. Side effects
and adverse events (AEs) are tabulated and compared across treatment conditions using ANOVA or Chi-square. Subjective and cardiovascular effects produced by IV cocaine and placebo during treatment with nepicastat are compared to those produced during treatment with placebo using repeated measures (time being the repeated measure) analysis of variance (ANOVA), peak effect one-way ANOVA, and if indicated, area under the curve ANOVA.

EXAMPLE 7

[0187] Nepicastat is used in conjunction with psychosocial interventions, including but not limited to contingency management/vouchers, general cognitive behavioral therapy, relapse prevention, dialectical behavior therapy, individual drug counseling, group drug counseling, 12-step facilitation, noncontingency management, wait listing, motivational enhancement and combinations of two or more of such interventions, for the prevention or treatment of a patient for addiction to drugs, such as cocaine.

[0188] The treatment of the patient is as described in Example 6, with the addition of psychosocial interventions. The psychosocial intervention can occur concurrently with the treatment of the patient with nepicastat, or the pharmacological treatment and the psychosocial treatment can occur sequentially with some overlap. Psychosocial therapy is conducted daily for some patients, weekly for other patients, and monthly or longer for other patients, where the selection of the frequency of psychosocial therapy depends on the initial assessment of the patient.

[0189] The usage of nepicastat enhances the results of such interventions by making such interventions more effective, less stressful, more rewarding, less time consuming for the same effect or, with equal time consumption, more likely to generate a larger beneficial effect. The patient undergoing the treatment self-reports the following:

1. mean maximum number of days or weeks abstinent throughout treatment;
2. mean percent of days abstinent throughout treatment;
3. percent of sample abstinent for 3 or more weeks throughout treatment;
4. percent of sample demonstrating post-treatment and/or clinically significant abstinence; and
5. post-treatment scores on the drug scale of the Addiction Severity Index.
In addition, objective measure of abstinence or reduced drug use are obtained by mean number of negative screens throughout treatment, mean percent or negative screens throughout treatment, and percent of sample demonstrating clinically significant abstinence.

The combination of subjective and objective data thus collected shows a decrease in the frequency or amount of unwanted or illicit drug usage or both. Further, patients undergoing treatment with nepicastat in combination with behavioral therapy show a larger percentage of the patients complete the therapy compared with those patients enrolled in behavioral therapy alone where one-third to one-half of patients will "drop out" before completing therapy.

Thus, the treatment of patients with nepicastat in combination with psychosocial therapy results in a clinically significant improvement of 1-100% in effect size with a stable or higher and smaller percentage confidence interval.

Nepicastat may be dosed acutely or chronically, before, during or after one or more episodes or types of psychosocial interventions, and in any convenient dosing form of nepicastat, including those for administration by enteral or parenteral routes or by drug delivery devices.

One additional benefit of nepicastat therapy is diagnostic as well as therapeutic. Although nepicastat has therapeutic utility in the absence of psychosocial interventions, a response to nepicastat can provide useful indications as to whether a patient is more or less likely to receive additional benefit from one or more modes of psychosocial intervention and, of particular interest, which one of the psychosocial approaches is most likely to add further benefit.

It will be readily apparent to one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the methods and applications described herein are suitable and may be made without departing from the scope of the invention or any embodiment thereof. While the invention has been described in connection with certain embodiments, it is not intended to limit the invention to the particular forms set forth, but on the contrary, it is intended to cover such alternatives, modifications and equivalents as may be included within the spirit and scope of the invention as defined by the following claims.
What is claimed is:

1. A method of treating a patient suffering from or susceptible to at least one symptom of abuse of, dependence on, or withdrawal from at least one substance, the method comprising administering to the human patient a therapeutically effective amount of nepicastat, or a prodrug thereof or a pharmaceutically acceptable salt thereof, in combination with psychosocial therapy.

2. The method of claim 1, wherein the at least one substance is a drug of abuse or a medication.

3. The method of claim 2, wherein the drug of abuse is selected from the group consisting of a psychostimulant agent, an opioid, an hallucinogen, an inhalant, a sedative, a tranquilizer, a hypnotic, an anxiolytic, and an illicit substance.

4. The method of claim 3, wherein the psychostimulant agent is a beta-phenylisopropylamine derivative.

5. The method of claim 4, wherein the beta-phenylisopropylamine derivative is selected from the group consisting of amphetamine, dextroamphetamine, and methamphetamine.

6. The method of claim 3, wherein the psychostimulant agent is selected from the group consisting of 3,4-methylenedioxymethamphetamine ("ecstasy"), phenmetrazine, methylphenidate, diethylpropion, pemoline, mazindol, (-) cathione, lisdexamfetamine, modafinil, and fenfluramine.

7. The method of claim 3, wherein the opioid is selected from the group consisting of Lortab, Tramadol, heroin, methadone, hydrocodone, and oxycodone.

8. The method of claim 3, wherein the hallucinogen is selected from the group consisting of psilocybin, a hallucinogenic mushroom, lysergic acid diethylamide (LSD), phencyclidine (PCP), and ketamine.

9. The method of claim 3, wherein the inhalant is selected from the group consisting of benzene, toluene, o-xylene, m-xylene, p-xylene, ethylbenzene, fluorobenzene, o-difluorobenzene, 1,3,5-trifluorobenzene, 1,2,4-trifluorobenzene, pentafluorotoluene, pentafluorobenzene, and perfluorobenzene.

10. The method of claim 2, wherein the medication is selected from the group consisting of an anesthetic, an analgesic, an anticholinergic agent, an antihistamine, a muscle relaxant, a nonsteroidal anti-inflammatory medication, an over the counter medication, and an antidepressant medication.
11. The method of claim 2, wherein the drug of abuse is cocaine, alcohol, caffeine, opium, cannabinoid, cannabis, benzodiazapine carisprodol, tobacco, nicotine, Vicodin, Lorcar, Percocet, Percodan, or Tylox.

12. The method of claim 11, wherein the drug of abuse is cocaine and nepiccastat reduces at least one symptom of cocaine abuse and dependence in the patient selected from the group consisting of attention deficit hyperactivity disorder, euphoria, increased energy, excitement and sociability, less hunger and fatigue, a marked feeling of physical and mental strength, decreased sensation of pain, bronchitis, shortness of breath, chest pain, heart palpitations, arrhythmia, cardiomyopathy, heart attack, dilated pupils, nausea, vomiting, headache, vertigo, dizziness, anxiety, psychosis, confusion, nasal irritation, nasal crusting, recurrent nosebleeds, nasal stuffiness, facial pain, dysphoria, and craving for cocaine.

13. The method of claim 11, wherein the drug of abuse is cocaine and nepiccastat increases at least one negative subjective symptom of cocaine abuse and dependence.

14. The method of claim 11, wherein the drug of abuse is cocaine and nepiccastat reduces at least one symptom of cocaine withdrawal selected from the group consisting of fatigue, lack of pleasure, depression, irritability, sleep disorders, increased appetite, psychomotor retardation, agitation, extreme suspicion, and craving for cocaine.

15. The method of claim 1, wherein nepiccastat is administered in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

16. The method of claim 15, wherein the excipient is suitable for oral administration.

17. The method of claim 16, wherein the excipient is a solid.

18. The method of claim 17, wherein the composition is in the form of a tablet, a capsule, or a soft-gel capsule.

19. The method of claim 16, wherein the excipient is liquid.

20. The method of claim 19, wherein the excipient is suited to intravenous, intramuscular, or subcutaneous administration.

21. The method of claim 20, wherein the excipient is suited to transdermal administration.

22. The method of claim 1, wherein the therapeutic amount of nepiccastat is from about 80 mg to about 400 mg.

23. The method of claim 22, wherein the therapeutic amount of nepiccastat is from about 160 mg to about 240 mg.
24. The method of claim 1, wherein the method further comprises co-administering a therapeutically effective amount of at least one other agent selected from a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), a norepinephrine reuptake inhibitor (NRI), a norepinephrine-dopamine reuptake inhibitor (NDRI), a serotonin 5-hydroxytryptamineA (5HT1A) antagonist, a dopamine β-hydroxylase inhibitor, an adenosine receptor antagonist, an adenosine A2A receptor antagonist, a monoamine oxidase inhibitor (MAOI), a monoamine oxidase B inhibitor, a sodium channel blocker, a calcium channel blocker, a central and peripheral alpha adrenergic receptor antagonist, a central alpha adrenergic agonist, a central or peripheral beta adrenergic receptor antagonist, a NK-I receptor antagonist, a corticotropin releasing factor (CRF) antagonist, an atypical antidepressant/antipsychotic, a tricyclic, an anticonvulsant, a glutamate antagonist, a gamma-aminobutyric acid (GABA) agonist, a GABA metabolism enzyme inhibitor, a GABA synthesis activator, a partial dopamine D2 agonist, a dopamine metabolism enzyme inhibitor, a catechol-O-methyl-transferase inhibitor, an opioid receptor antagonist, a mood stabilizer, a direct or indirect dopamine agonist, a partial 5HT1 agonist, a serotonin 5HT2 antagonist, an opioid, a carboxylase inhibitor, a partial opioid agonist, a partial nicotinic agonist, and an inhalant.

25. The method of claim 1, wherein the method further comprises co-administering a therapeutically effective amount of at least one other agent selected from benzodiazepine, levodopa, carisprodol, modafinil, acamprosate, gamma-butyrolactone, gamma-hydroxybutyrate, opium, psilocybin, hallucinogenic mushroom, tobacco, and nicotine.

26. The method of claim 1, wherein the method further comprises administering a therapeutically effective amount of nepicastat in conjunction with a psychosocial intervention.

27. The method of claim 1, wherein nepicastat is administered before, during or after psychosocial therapy.

28. The method of claim 1, wherein the psychosocial therapy is selected from the group consisting of contingency management/vouchers, general cognitive behavioral therapy, relapse prevention, role-playing, dialectical behavior therapy, individual drug counseling, group drug counseling, 12-step facilitation, noncontingency management, wait listing, motivational enhancement, informal psychosocial intervention by friends or family, and combinations thereof.
### Table 1

<table>
<thead>
<tr>
<th>ENZYME OR RECEPTOR</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (enzyme) or pKi (receptor)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzymes</strong></td>
<td></td>
</tr>
<tr>
<td>Dopamine-β-hydroxylase (bovine)</td>
<td>8.5 nM</td>
</tr>
<tr>
<td>Dopamine-β-hydroxylase (human)</td>
<td>9 nM</td>
</tr>
<tr>
<td>Acetyl CoA Synthetase</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>Acyl-CoA: Cholesterol Acptransferase</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt;-Calmodulin Protein Kinase II</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>Cyclooxygenase-I</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>HMG-CoA Reductase</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>Neutral Endopeptidase (human)</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>Nitric oxide synthase (constitutive)</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>Nitric oxide synthase (inducible)</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>Phosphodiesterase III (human)</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>Phospholipase A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td>Protein Kinase (non-selective)</td>
<td>&lt; 10 μM</td>
</tr>
<tr>
<td><strong>Receptors</strong></td>
<td></td>
</tr>
<tr>
<td>α&lt;sub&gt;1A&lt;/sub&gt;, α&lt;sub&gt;1B&lt;/sub&gt; adrenoceptors</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>α&lt;sub&gt;2A&lt;/sub&gt;, α&lt;sub&gt;2B&lt;/sub&gt; adrenoceptors</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>β&lt;sub&gt;1&lt;/sub&gt;, β&lt;sub&gt;2&lt;/sub&gt; adrenoceptors</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt; muscarinic receptors</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>D&lt;sub&gt;1&lt;/sub&gt;, D&lt;sub&gt;2&lt;/sub&gt; dopamine receptors</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>μ-opioid receptors</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;, 5-HT&lt;sub&gt;2A&lt;/sub&gt;, 5-HT&lt;sub&gt;2C&lt;/sub&gt; serotonin receptors</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>
Figure 2

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>N</th>
<th>CONCENTRATION OF NEPICASTAT (µM)</th>
<th>% INHIBITION OF ENZYME</th>
<th>IC_{50} * (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine hydroxylase</td>
<td>2</td>
<td>100</td>
<td>11</td>
<td>&gt;100</td>
</tr>
<tr>
<td>NO synthase (constitutive)</td>
<td>2</td>
<td>10</td>
<td>6</td>
<td>&gt;10</td>
</tr>
<tr>
<td>NO synthase (inducible)</td>
<td>2</td>
<td>10</td>
<td>-1</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Phosphodiesterase III</td>
<td>2</td>
<td>100</td>
<td>-9</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Phospholipase A$_2$</td>
<td>2</td>
<td>300</td>
<td>3</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Neutral endopeptidase (human)</td>
<td>2</td>
<td>10</td>
<td>-12</td>
<td>&gt;10</td>
</tr>
<tr>
<td>CA$^{2+}$/calmodulin dependent protein kinase II</td>
<td>2</td>
<td>100</td>
<td>53</td>
<td>~100</td>
</tr>
<tr>
<td>Acetyl CoA synthetase</td>
<td>2</td>
<td>100</td>
<td>-4</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Acyl CoA-cholesterol acyl transferase</td>
<td>2</td>
<td>100</td>
<td>6</td>
<td>&gt;100</td>
</tr>
<tr>
<td>HMG-CoA reductase</td>
<td>2</td>
<td>30</td>
<td>16</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Protein kinase (non-selective)</td>
<td>2</td>
<td>300</td>
<td>39</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Cyclooxygenase-I</td>
<td>2</td>
<td>300</td>
<td>44</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

* Approximate estimation of IC_{50}
Figure 3

t tests – Means: Difference between two dependent means (matched pairs)
Tail(s) = Two, a err prob = 0.05

Power (1-8 err prob)

- = 0.6
- = 0.65
- = 0.7
- = 0.75

Effect size dz

Total Sample Size