various pain syndromes, including, but not limited to, myofascial pain, muscle tension headache, and chronic post operative wound syndromes, based on retrospective and prospective analysis in the application of botulinum toxin for the treatment of pain syndromes involving the head and neck.

SUMMARY

[0014a] In one aspect, there is provided use of botulinum toxin in the manufacture of a medicament for treating a sleep disorder in a subject having an abnormality in at least one brain neurotransmitter in at least one region of the brain in the upper brainstem or medial hemispheres, wherein the region of the brain with abnormal activity in at least one brain neurotransmitter is identified using a brain scan or spectral Magnetic resonance imaging (MRI) scan;
wherein the botulinum toxin is to be injected in an effective amount into an extra cranial region of the head, wherein the extra cranial region of the head is at least one selected from a sinus, nasal mucosa, oropharynx, and nasopharynx; and wherein the botulinum toxin is allowed to diffuse to the region of the brain in the upper brainstem or medial hemispheres with abnormal neurotransmitter activity and blocks neurotransmission of the at least one neurotransmitter.

[0015] The present disclosure provides methods of treating depressive, anxiety and sleep disorders comprising the administration of pharmaceutical compositions comprising neurotoxins.

[0016] The present disclosure provides methods for treating depression comprising the steps of: a) identifying a subject with a depressive disorder or identifying a subject with one or more symptoms of a depressive disorder; and b) administering an effective amount of a composition comprising a botulinum toxin and a pharmaceutically acceptable carrier to said subject.

[0017] The present disclosure also provides methods of treating anxiety comprising the steps of: a) identifying a subject with an anxiety disorder or identifying a subject with at least one symptom of an anxiety disorder; and b) administering an effective amount of a composition comprising a botulinum toxin and a pharmaceutically acceptable carrier to said subject.

[0018] The present disclosure also provides methods of treating sleep disorders comprising the steps of: a) identifying a subject with a sleep disorder or identifying a subject exhibiting at least one symptom of a sleep disorder; and b) administering an effective amount of a composition comprising a botulinum toxin and a pharmaceutically acceptable carrier to said subject.

[0019] The present disclosure also provides methods of treating circadian rhythm disorders comprising the steps of: a) identifying a subject with a circadian rhythm disorder; and b) administering an effective amount of a composition comprising a botulinum toxin and a pharmaceutically acceptable carrier to said subject.

[0020] The present disclosure also provides methods of delivering botulinum toxin across a blood-brain barrier comprising the steps of: a) identifying a subject with at least one neuropsychiatric disorder; and b) administering a composition comprising a neurotoxin and a pharmaceutically acceptable carrier to said subject in an amount sufficient to deliver said neurotoxin across the blood-brain barrier.

[0021] The present disclosure also provides methods of delivering botulinum toxin across a blood-brain barrier comprising the steps of: a) identifying a subject with at least one neuropsychiatric disorder; and b) administering a composition comprising a neurotoxin and a pharmaceutically acceptable carrier to said subject in an amount sufficient to deliver said neurotoxin across the blood-brain barrier, wherein said administration of said injection of neurotoxin blocks at least one neurotransmitter. In a preferred example, the neurotransmitter is acetylcholine.

[0022] The present disclosure also provides methods of treating an anxiety disorder comprising the steps of: a) identifying a subject with at least one anxiety disorder or identifying a subject with one or more symptoms of an anxiety disorder; and b) administering to said subject a composition comprising a neurotoxin and a pharmaceutically acceptable carrier said composition is delivered across the blood-brain barrier in an amount sufficient to decrease cholinergic neuron transmission.

[0023] The present disclosure also provides methods of treating a sleep disorder comprising the steps of: a) identifying a subject with at least one sleep disorder or identifying a subject with one or more symptoms of a sleep disorder; and b) administering to said subject a composition comprising a neurotoxin and a pharmaceutically acceptable carrier said composition is delivered across the blood-brain barrier in an amount sufficient to decrease cholinergic neuron transmission. In a preferred example, the composition decreases choline acetyltransferase activity. In another preferred example, the composition decreases the synthesis of acetylcholine. In another preferred example, the sleep disorder is insomnia. In another preferred example, the sleep disorder is narcolepsy, restless leg syndrome or sleep apnea.

[0024] The present disclosure also provides methods of treating a circadian rhythm disorder comprising the steps of: a) identifying a subject with at least one circadian rhythm disorder or identifying a subject with one or more symptoms of a circadian rhythm disorder; and b) administering to said subject a composition comprising a neurotoxin and a pharmaceutically acceptable carrier said composition is delivered across the blood-brain barrier in an amount sufficient to decrease cholinergic neuron transmission. In a preferred example, the composition decreases choline acetyltransferase activity. In another preferred example, the composition decreases the synthesis of acetylcholine.

[0025] The present disclosure also provides methods of treating a depressive disorder comprising the steps of: a) identifying a subject with at least one depressive disorder or identifying a subject with one or more symptoms of a depressive disorder; and b) administering to said subject a composition comprising a neurotoxin and a pharmaceutically acceptable carrier said composition is delivered across the blood-brain barrier in an amount sufficient to decrease cholinergic neuron transmission. In a preferred example, the composition decreases choline acetyltransferase activity. In another preferred example, the composition decreases the synthesis of acetylcholine.

[0026] The present disclosure provides methods of selecting a subject for the treatment of pain with botulinum toxin, comprising the step of identifying a subject suffering from a pain syndrome and a condition selected from the group consisting of a depressive disorder, an anxiety disorder and a sleep disorder, wherein the identification of a subject with a pain syndrome and a condition selected from the group consisting of a depressive disorder, an anxiety disorder and a sleep disorder is predictive of increased responsiveness to the treatment of pain with botulinum toxin. In a preferred example, the pain syndrome is any one or a combination of the pain syndromes selected from the group consisting of: myofacial pain; migraine headache; post-operative wound pain; sinusitis-related headaches; muscle tension headaches; post-traumatic headaches; cluster headaches; temporal mandibular joint syndrome; fibromyalgia; atypical facial pain; post incisional wound pain; cervical radiculopathy; and whiplash.

[0027] In another example of the present disclosure, subjects suffering from a condition selected from the group consisting of a depressive disorder, an anxiety disorder and a sleep disorder were identified by determining that a subject has a medical history of a depressive disorder, an anxiety disorder, or a sleep disorder, respectively.

[0028] The present disclosure also provides methods of identifying a subject with increased responsiveness to treating a pain disorder with botulinum toxin, comprising the step of screening a population of subjects to identify those subjects that suffer from a pain disorder and a condition selected from the group consisting of a depressive disorder, an anxiety disorder and a sleep disorder, wherein the identification of a subject with a pain syndrome and a condition selected from the group consisting of a depressive disorder, an anxiety disorder and a sleep disorder is predictive of increased responsiveness to the treatment of pain with botulinum toxin. In a preferred example, the pain syndrome is any one or a combination of the pain syndromes selected from the group consisting of: myofacial pain; migraine headache; post- operative wound pain; sinusitis-related headaches; muscle tension headaches; post-traumatic headaches; cluster headaches; temporal mandibular joint syndrome; fibromyalgia; atypical facial pain; post incisional wound pain; cervical radiculopathy; and whiplash.

[0029] The present disclosure provides a method that comprises the steps of identifying or diagnosing a pain syndrome; diagnosing or eliciting a history of a condition selected from the group consisting of a depressive disorder, an anxiety disorder and a sleep disorder; and classifying the identified pain syndrome as one with increased responsiveness to treatment with botulinum toxin. In one example, a pain syndrome is identified according to the International Headache Classification System (The International Headache Society (I.H.S.)).

[0030] The present disclosure provides a method of selecting patients for the treatment of human headache disorders with a botulinum toxin based pharmaceutical, comprising diagnosing headache type occurring in a patient suffering from a depressive disorder, an anxiety disorder, obsessive compulsive behavioral traits, or a sleep disorder and administering a therapeutically effective amount of botulinum toxin. In one example the headache disorder is migraine, tension headache, combined tension and migraine headache, myofascial headache, sinus

headache, headache associated with temporal mandibular joint syndrome, headache associated with fibromyalgia, or headache associated with neuralgia.

[0031] The present disclosure also provides a method of selecting patients for the treatment of human facial pain disorders with a botulinum toxin based pharmaceutical, comprising diagnosing a facial pain disorder occurring in a patient suffering from a depressive disorder, an anxiety disorder, obsessive compulsive behavioral traits, or a sleep disorder and administering a therapeutically effective amount of botulinum toxin. In one example, the facial pain disorder is trigeminal neuralgia, the facial pain disorder is associated with bruxism, or the facial pain disorder is post-operative chronic surgical wound pain.

[0032] The compositions of the present disclosure comprise botulinum toxin and a pharmaceutically acceptable carrier. In a preferred example, the botulinum toxin is immunotype A, B, C, D, E, F, or G. In a more preferred example, the botulinum toxin is botulinum toxin type A from Hall strain Clostridium botulinum.

[0033] The methods of the present disclosure may preferably be practiced by administering the botulinum toxin compositions by injection, including transcutaneous, percutaneous, subcutaneous, intraperitoneal, transdermal, intramuscular and intraosseous, but expressly not intracranial, transcranial, intrathecal or intraspinal injection or administration. In one example, there are at least two injection sites. In another example, the injections are multifocal. The botulinum toxin may be preferably administered to the forehead, scalp or neck or other locations such as the periocular region and other areas of the face that enhance venous drainage from the site of administration to the central nervous system (CNS). In another example, the botulinum toxin may be administered to the soft tissues outside the neurocranium. In another example, the botulinum toxin may be administered in locations that maximize uptake by the portal hypophyseal drainage.

[0034] Examples of compounds and formulations which can be used in the present disclosure include botulinum toxin stabilized with a protein such as serum albumin or hyaluronidase. In a preferred example, the serum albumin or hyaluronidase is recombinant.

In another example, the serum albumin is present at a concentration of greater than 500 .mu.g/100 LD_{50} units botulinum toxin. The botulinum toxin pharmaceutical may be further stabilized with a simple stabilizing sugar or polysaccharide (e.g. sucrose, lactose or trehalose). The botulinum toxin is preferably a monocomponent neurotoxin of a molecular weight of 150,000 Daltons that is free of complex botulinum toxin proteins. The compositions disclosed herein may also comprise a polyethylene glycol polymer; a vegetable fat-based nanoemulsion; and any nanoemulsion using one or more monounsaturated or polyunsaturated oils. In a preferred example, the botulinum toxin compositions used in the methods of the present disclosure are formulated to enhance penetration of the botulinum toxin into and through the skin.

[0035] Recent advances in pharmaceutical technology have focused on enhanced delivery systems such as transdermal or transcutaneous delivery systems. Such systems are thought to be more convenient and associated with less pain. The problems associated with such systems include poor penetration of materials through the epidermis and dermis. Hyaluronidase offers improved penetration.

[0036] A pharmaceutical composition comprising botulinum neurotoxin, hyaluronidase, and sugars (both simple and oligosaccharides) is suitable for the methods of the present disclosure. The botulinum toxin pharmaceutical formulations suitable for use in for the methods of the present disclosure are preferably devoid of any human blood or recombinant blood products and will be either stabilized in flash or freeze dried form. The pH is preferably between pH 3.0 to 7.4 and the preparation may be used as an injection, transdermal or topical agent. The botulinum toxin pharmaceutical formulations suitable for use in for the methods of the present disclosure may be administered by injection, needleless delivery systems, and methods requiring disruption techniques such as electroporation, sonication, and high pressure air gas flow injection or in the form of a micro-needle. Micro-needles are generally from 150 to 600 microns. Furthermore, the botulinum toxin pharmaceutical formulations suitable for use in for the methods of the present disclosure may further comprise polycationic proteins.

[0037] Currently, hyaluronidase is available at a number of specific activities. For example, sheep based materials can have a specific activity of 1,500 Upper mg or 1.5 Upper

mcg. Typically, 75-300 U are used for injection, such as conducted with peri-bulbar anesthesia for intra-ocular surgery. This would correspond to about 100-450 mg in mass of enzymatic protein, enough to act as a stabilizing excipient.

[0038] Prior studies have shown that a protein excipient, such as human serum albumin, can stabilize the botulinum toxin. Test studies conducted demonstrate that hyaluronidase also stabilizes the botulinum toxin at the same levels observed for the human serum albumin.

[0039] The compositions disclosed herein may be such that the doses are formulated into a concentration suitable for administration as an eye drop to facilitate transconjunctival penetration for the treatment of ocular surface diseases. The compositions disclosed herein may be such that the LD_{50} units range from 1.25 U-3,000 units of botulinum toxin type A. The compositions disclosed herein may be such that the LD_{50}units range from 1.25-20,000 U of botulinum type B. The compositions disclosed herein may be such that the formulation is delivered into the nose or oral cavity as an aerosol to facilitate intracranial delivery of a botulinum toxin based pharmaceutical. The compositions disclosed herein may be such that the formulation is delivered into the ear canal as an aerosol to facilitate intracranial delivery of a botulinum based pharmaceutical

[0040] The present disclosure provides methods for delivering a botulinum toxin based pharmaceutical to the central nervous system of a subject by any injection or topical application method, except intracranial, transcranial, intrathecal or intraspinal injection, in a therapeutically effective amount sufficient to decrease at least one central nervous system neurotransmitter when compared to an untreated subject. In a preferred example, the at least one central nervous system neurotransmitter is glutamate, norepinephrine, or acetyl-choline. In a more preferred example, the at least one central nervous system neurotransmitter is glutamate. In another example, the methods of the present disclosure decrease at least one central nervous system neurotransmitter when compared to an untreated subject sufficiently to reduce at least one symptom of insomnia, a sleep disorder, an anxiety disorder, a depressive disorder, dysmenorrhea, an appetite or eating disorder, or a seizure disorder. In a preferred example the seizure disorder is generalized, focal motor, or partial complex.

[0041] Glutamate is a neurotransmitter that exhibits endogenous neurotoxic activity that is observed in a number of neurodegenerative diseases and disorders, vascular accidents such as stroke and in seizure disorders. For example, subjects with mild to moderate dementia and probable Alzheimer's Disease have been shown to exhibit elevated levels of glutamate in the central nervous system. Elevated glutamate in the central nervous system is reflective of increased glutamatergic activity in the early stages of Alzheimer's Disease. The progressive neuronal loss observed in Alzheimer's Disease and other neurodegenerative disorders and diseases correlate with elevated glutamate and the increased excitotoxicity associated with elevated levels of this neurotransmitter.

[0042] The present disclosure provides methods for reducing glutamate levels in the central nervous system, the brain or portions of the brain comprising the step of administering a botulinum toxin pharmaceutical to a subject, by any injection or topical application method, except intracranial, transcranial, intrathecal or intraspinal injection, in an amount sufficient to reduce glutamate levels in the central nervous system, the brain, or portions of the brain compared to an untreated subject.

[0043] The present disclosure provides methods for neuroprotection comprising the step of administering a botulinum toxin pharmaceutical to a subject, by any injection or topical application method, except intracranial, transcranial, intrathecal or intraspinal injection, in an amount sufficient to reduce neuronal loss in the central nervous system, the brain or portions of the brain compared to an untreated subject.

[0044] The present disclosure also provides methods for delivering a botulinum toxin based pharmaceutical to the central nervous system of a subject by injection into the nasal sinuses in a therapeutically effective amount sufficient to decrease at least one central nervous system neurotransmitter when compared to an untreated subject. In a preferred example, the at least one central nervous system neurotransmitter is glutamate, norepinephrine, or acetyl-choline. In a more preferred example, the at least one central nervous system neurotransmitter is glutamate. In another example, the methods of the present disclosure

decrease at least one central nervous system neurotransmitter when compared to an untreated subject sufficiently to reduce at least one symptom of insomnia, a sleep disorder, an anxiety disorder, a depressive disorder, dysmenorrhea, or a seizure disorder. In a preferred example the seizure disorder is generalized, focal motor, or partial complex.

[0045] The present disclosure also provides methods for delivering a botulinum toxin based pharmaceutical to the central nervous system of a subject by any injection or topical application method, except intracranial, transcranial, intrathecal or intraspinal injection, in a therapeutically effective amount sufficient to decrease at least one central nervous system neurotransmitter when compared to an untreated subject. In a preferred example, the at least one central nervous system neurotransmitter is glutamate, nor-epinephrine, or acetyl-choline. In a more preferred example, the at least one central nervous system neurotransmitter is glutamate. In another example, the methods of the present disclosure decrease at least one central nervous system neurotransmitter when compared to an untreated subject sufficiently to reduce an agitated behavior associated with mental retardation, schizophrenia, Huntington's Chorea or Alzheimer's Disease.

[0046] The present disclosure also provides methods for delivering a botulinum toxin based pharmaceutical to the central nervous system of a subject by any injection or topical application method, except intracranial, transcranial, intrathecal or intraspinal injection, in a therapeutically effective amount sufficient to decrease at least one central nervous system neurotransmitter when compared to an untreated subject. In a preferred example, the at least one central nervous system neurotransmitter is glutamate, nor-epinephrine, or acetyl-choline. In a more preferred example, the at least one central nervous system neurotransmitter is glutamate. In another example, the methods of the present disclosure decrease at least one central nervous system neurotransmitter when compared to an untreated subject sufficiently to reduce at least one symptom of a neurodegenerative disease associated with inflammation.

[0047] The present disclosure also provides for the use of botulinum toxin or a botulinum toxin composition of the present disclosure in the production of a medicament for the treatment of any one of the disorders, diseases or conditions disclosed herein, including depressive disorders,

I claim:

1. Use of botulinum toxin in the manufacture of a medicament for treating a sleep disorder in a subject having an abnormality in at least one brain neurotransmitter in at least one region of the brain in the upper brainstem or medial hemispheres,

wherein the region of the brain with abnormal activity in at least one brain neurotransmitter is identified using a brain scan or spectral Magnetic resonance imaging (MRI) scan;

wherein the botulinum toxin is to be injected in an effective amount into an extra cranial region of the head,

wherein the extra cranial region of the head is at least one selected from a sinus, nasal mucosa, oropharynx, and nasopharynx; and

wherein the botulinum toxin is allowed to diffuse to the region of the brain in the upper brainstem or medial hemispheres with abnormal neurotransmitter activity and blocks neurotransmission of the at least one neurotransmitter.

2. The use of claim 1, wherein the neurotransmitter is glutamate.

3. The use of claim 1, wherein the neurotransmitter is acetyl choline.

4. The use of claim 1, wherein the neurotransmitter is GABA.

5. The use of claim 1, wherein the neurotransmitter is nor epinephrine.

6. The use of claim 1, wherein said medicament is to be used with an implantation device to enhance penetration of the botulinum toxin to the brain.

7. The use of claim 6, wherein said device is a hollow pin.

8. The use of claim 7, wherein said hollow pin is composed of titanium, ceramic, and/or plastic.