METHODS OF TREATING SIALORRHEA WITH BUPROPION AND ITS METABOLITES

Abstract: Methods of treating sialorrhea in a patient by administering bupropion, bupropion metabolites or pharmaceutically acceptable salts thereof are disclosed. In certain embodiments, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, bupropion metabolite and a pharmaceutically acceptable salt is administered to a patient to treat sialorrhea.
A. Title: METHODS OF TREATING SIALORRHEA WITH BUPROPION AND ITS METABOLITES

B. Cross Reference


C. Government Interests - Not Applicable

D. Parties to a Joint Research Agreement - Not Applicable

E. Incorporation by Reference of Material Submitted on a Compact Disc - Not Applicable

F. Background

[0002] A variety of conditions and situations present the problem of undesirable amounts of saliva in the mouth of an individual. Classically, "sialorrhea" has been defined as "excess production of saliva, or increased retention of saliva in the mouth" or "saliva beyond the margin of the lip", i.e., drooling, although the term sialorrhea has sometimes more loosely been used to describe "excessive saliva secretion". Sialorrhea is a well known, but often not discussed, condition that affects patients with various neurological diseases. Sialorrhea also affects individuals with mental and developmental disabilities, those who have sustained various brain injuries, and individuals who have had a stroke. Sialorrhea may also occur as the result of neuromuscular dysfunction, sensory dysfunction, motor dysfunction, parkinsonism, pseudobulbar palsy, bulbar palsy, multiple system atrophy, corticobasal degeneration, motor neuron diseases, and neurodegenerative diseases. Several other situations predispose the development of sialorrhea due to the imperfect control of orofacial, head, and neck musculature, as is commonly found in patients with cerebrovascular accidents, head injuries, severe dental malocclusion, and mental retardation. Drug reactions involving tranquilizers, anticonvulsants, and anticholinesterases (e.g., clozapine and other drugs used to treat schizophrenia, and remoxipride) can also aggravate sialorrhea by causing hypersecretion of saliva. Sialorrhea affects over 3 million people annually.
[0003] Depending on its degree, drooling can result in social and medical disability, impaired speech, or serious feeding difficulties. Unable to manage their oral secretions, affected persons are at increased risk of aspiration pneumonia, skin maceration, and infection. Care may be compromised since the frequent suctioning and cleaning that are required to maintain proper hygiene can become very burdensome.

[0004] Saliva is produced by both the major and minor salivary glands. There are three pairs of major salivary glands: the parotid, submandibular, and sublingual glands. These glands produce from 1-1.5 liters of saliva daily in a circadian rhythm: in the resting state 70% of the saliva is from the submandibular glands, 25% is from the parotid glands, and 5% is from the sublingual glands. Minor salivary glands located on the palate, buccal mucosa, and tongue produce modest amounts of saliva. The secretory innervation of the salivary glands is primarily under the control of the parasympathetic nervous system. Stimulation of the parasympathetic system causes profuse secretion of saliva. The resting secretory rate may increase by 5 to 10-fold upon stimulation by olfactory, tactile, and gustatatory nerves.

[0005] Radiation therapy has been shown to produce glandular atrophy and decreases secretions; however, the dose required for atrophy may produce xerostomia, and the potential risk of secondary malignancy exists. In most cases, it seems inappropriate to substitute the dangers of radiation for the alleviation of drooling. Currently there is no completely safe therapy to resolve sialorrhea satisfactorily in all patients without significant side effects. Clearly the need remains for an effective, easily administered treatment for sialorrhea and other situations where it is desirable to control or temporarily decrease saliva production.

G. Brief Summary of the Invention

[0006] In one embodiment, methods of treating sialorrhea by administering bupropion and bupropion metabolites and derivatives are disclosed. In certain embodiments, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, a bupropion metabolite, a bupropion derivative or a pharmaceutically acceptable salt thereof is administered to a patient to treat sialorrhea.

[0007] In certain embodiments, bupropion metabolites comprise bupropion metabolite isomers. In certain embodiments, the bupropion metabolite isomers may have differential stereo-isomer activity.
In certain embodiments, exemplary bupropion metabolites include, but are not limited to, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1-dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol) amino] -1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol) amino]-1-propanone.

In certain embodiments, exemplary pharmaceutically acceptable salts and solvates thereof include, but are not limited to, (+)-2-(tert-butylamino)-3'-chloropropiophenone hydrochloride, (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, (R, R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, (+/-)-(2R*,3R*)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride, (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride and (25,35)-hydroxybupropion.

Embodiments are also directed to methods of treating drug-induced sialorrhea by administering bupropion, a bupropion metabolite or a pharmaceutically acceptable salt thereof to a patient. In certain embodiments, the bupropion, metabolite thereof or derivative thereof is administered in a therapeutically effective amount. In certain embodiments, sialorrhea is induced by a drug, including, but not limited to, for example psychotropics, antipsychotics, mercury, iodide, copper, arsenic, bitters, carbidopa-levodopa, carbidopa, levodopa, clozapine, clozapine metabolites and clozapine derivatives. In yet another embodiment, sialorrhea is induced by a drug including, but not limited to, for example, dopamine agonists, antipsychotic agents, acetylcholine esterase inhibitors, NMDA receptor antagonists, benzodiazepines, triptans, ethionamide, cholinomimetics and indirect cholinergic agonists, yohimbine, trazodone, organophosphates and combinations thereof.

In certain embodiments, exemplary dopamine agonists include, but are not limited to levodopa, carbidopa, bromocriptine, cabergoline, pergolide, pramipexole, ropinirole, apomorphine, rotigotine and combinations thereof.

In certain embodiments, exemplary antipsychotic agents include, but are not limited to, quetiapine fumarate, paliperidone, risperidone, fluspirilene, remoxipride and combinations thereof.

In certain embodiments, exemplary acetylcholine esterase inhibitors include, but are not limited to Aricept, galanthamine, THA and combinations thereof.
In certain embodiments, exemplary NMDA receptor antagonists include, but are not limited to ketamine, ketamine stereoisomers, PCP and combinations thereof.

In certain embodiments, exemplary benzodiazepines include, but are not limited to diazepam, clonazepam, midazolam and combinations thereof. In yet another embodiment, triptans include, but are not limited to, sumatriptan.

Embodiments are also directed to methods of treating drug-induced sialorrhea in a patient by administering bupropion, a bupropion metabolite, a bupropion derivative or a pharmaceutically acceptable salt thereof to said patient. In certain embodiments, sialorrhea is induced by clozapine, a metabolite thereof or a derivative thereof. In certain embodiments, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, bupropion metabolite, bupropion derivative or a pharmaceutically acceptable salt is administered to a patient that is taking clozapine to treat the clozapine-induced sialorrhea.

Embodiments are also directed to methods of treating disease-associated sialorrhea by administering a therapeutically effective amount of bupropion, bupropion metabolites and bupropion derivatives. In certain embodiments, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, bupropion metabolite, bupropion derivative and a pharmaceutically acceptable salt is administered to a patient that has disease-associated sialorrhea. In certain embodiments, sialorrhea may be caused by diseases, including, but not limited to, retropharyngeal abscess, peritonsillar abscess, tonsillitis, Mononucleosis, sore throat, stomatitis, Chronic gastritis, Pregnancy, Maniacs, Hydrophobia, Parkinson's disease and cerebral palsy.

In yet another embodiment, sialorrhea may be caused by diseases, including, but not limited to, amyotrophic lateral sclerosis (ALS), Huntington's Chorea, myasthenia gravis, Parkinson's disease, bulbar paralysis, bilateral facial nerve palsy, hypoglossal nerve palsy and combinations thereof.

In a preferred embodiment, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, a bupropion metabolite, a bupropion derivative and a pharmaceutically acceptable salt is administered to a patient has Parkinson's disease to treat the Parkinson's-induced sialorrhea.

In yet another preferred embodiment, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, a bupropion metabolite, a
bupropion derivative and a pharmaceutically acceptable salt is administered to a patient that has cerebral palsy to treat the cerebral palsy-induced sialorrhea.

[0021] In a preferred embodiment, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, a bupropion metabolite, a bupropion derivative and a pharmaceutically acceptable salt is administered to a patient has ALS disease to treat the ALS-induced sialorrhea.

[0022] In a preferred embodiment, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, a bupropion metabolite, a bupropion derivative and a pharmaceutically acceptable salt is administered to a patient has Huntington's disease to treat the Huntington's-induced sialorrhea.

H. Detailed Description

[0023] Before the compositions and methods provided herein are described, it is to be understood that this invention is not limited to the particular processes, compositions, or methodologies described, as these may vary. Although any methods similar or equivalent to those described herein can be used in the practice or testing of embodiments of the present invention, the preferred methods are now described. It is also to be understood that the terminology used in the description is for the purpose of describing the particular versions or embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. All publications mentioned herein are incorporated by reference in their entirety to the extent to support the present invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0024] It must be noted that, as used herein, and in the appended claims, the singular forms "a", "an" and "the" include plural reference unless the context clearly dictates otherwise. As used herein, the term "about" means plus or minus 10% of the numerical value of the number with which it is being used. Therefore, about 50% means in the range of 45%-55%.

[0025] "Optional" or "optionally" may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the event occurs and instances where it does not.
[0026] "Administering" when used in conjunction with a therapeutic means to administer a therapeutic directly into or onto a target tissue or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. "Administering" a composition may be accomplished by, for example, oral administration, injection, infusion, absorption or by any method in combination with other known techniques.

[0027] The term "target", as used herein, refers to the material for which either deactivation, rupture, disruption or destruction or preservation, maintenance, restoration or improvement of function or state is desired. For example, diseased cells, pathogens, or infectious material may be considered undesirable material in a diseased subject and may be a target for therapy.

[0028] Generally speaking, the term "tissue" refers to any aggregation of similarly specialized cells which are united in the performance of a particular function.

[0029] The term "improves" is used to convey that the present invention changes either the appearance, form, characteristics and/or physical attributes of the tissue to which it is being provided, applied or administered. "Improves" may also refer to the overall physical state of an individual to whom an active agent has been administered. For example, the overall physical state of an individual may "improve" if one or more symptoms of a neurodegenerative disorder are alleviated by administration of an active agent.

[0030] As used herein, the term "therapeutic" means an agent utilized to treat, combat, ameliorate or prevent an unwanted condition or disease of a patient.

[0031] The terms "therapeutically effective amount" or "therapeutic dose" as used herein are interchangeable and may refer to the amount of an active agent or pharmaceutical compound or composition that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. A biological or medicinal response may include, for example, one or more of the following: (1) preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display pathology or symptoms of the disease, condition or disorder, (2) inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptoms of the disease, condition or disorder, and (3) ameliorating a disease, condition or disorder in an individual that is experiencing or exhibiting the pathology or symptoms of the disease, condition or disorder or reversing the pathology and/or
symptoms experienced or exhibited by the individual. For example, in the present embodiments, a therapeutically effective amount would be an amount that decreases the sialorrhea of the patient or stops the sialorrhea of the patient.

[0032] The term "unit dose" as used herein may be taken to indicate a discrete amount of the therapeutic composition which comprises a predetermined amount of the active compound. The amount of the active ingredient is generally equal to the dosage of the active ingredient which may be administered once per day, or may be administered several times a day (e.g. the unit dose is a fraction of the desired daily dose). The unit dose may also be taken to indicate the total daily dose, which may be administered once per day or may be administered as a convenient fraction of such a dose (e.g. the unit dose is the total daily dose which may be given in fractional increments, such as, for example, one-half or one-third the dosage).

[0033] The term "treat" may be taken to mean prophylaxis of a specific disorder, disease or condition, alleviation of the symptoms associated with a specific disorder, disease or condition and/or prevention of the symptoms associated with a specific disorder, disease or condition. For example, in the present embodiments, to treat sialorrhea would be to decrease the sialorrhea of the patient or stop the sialorrhea of the patient.

[0034] The term "patient" generally refers to any living organism to which compounds described herein are administered and may include, but is not limited to, any non-human mammal, primate or human. Exemplary non-human mammals include primates, cats, dogs, mice, rats, cows, sheep, pigs or other mammals. Such "patients" may or may not be exhibiting the signs, symptoms or pathology of the particular diseased state.

[0035] The term "pharmaceutical composition" shall mean a composition including at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan. A pharmaceutical composition may, for example, contain bupropion, a pharmaceutically acceptable salt of bupropion, or a metabolite of bupropion as the active ingredient.

[0036] For the purposes of this disclosure, a "salt" is any acid addition salt, preferably a pharmaceutically acceptable acid addition salt, including but not limited to, halogenic acid salts such as hydrobromic, hydrochloric, hydrofluoric and hydroiodic acid salt; an inorganic acid salt such as, for example, nitric, perchloric, sulfuric and phosphoric acid salt; an organic
acid salt such as, for example, sulfonic acid salts (methanesulfonic, trifluoromethan sulfonic, ethanesulfonic, benzenesulfonic or β- toluenesulfonic), acetic, malic, fumaric, succinic, citric, benzoic, gluconic, lactic, mandelic, mucic, pamoic, pantothenic, oxalic and maleic acid salts; and an amino acid salt such as aspartic or glutamic acid salt. The acid addition salt may be a mono- or di-acid addition salt, such as a di-hydrohalogenic, di-sulfuric, di-phosphoric or di-organic acid salt. In all cases, the acid addition salt is used as an achiral reagent which is not selected on the basis of any expected or known preference for interaction with or precipitation of a specific optical isomer of the products of this disclosure.

[0037] "Pharmaceutically acceptable salt" is meant to indicate those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a patient without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. (1977) J. Pharm. Sciences, Vol 6. 1-19, describes pharmaceutically acceptable salts in detail.

[0038] A "dose amount" as used herein, is generally equal to the dosage of the active ingredient which may be administered once per day, or may be administered several times a day (e.g. the unit dose is a fraction of the desired daily dose). The term "unit dose" as used herein may be taken to indicate a discrete amount of the therapeutic composition which comprises a predetermined amount of the active compound. The amount of the active ingredient is generally equal to the dosage of the active ingredient which may be administered once per day, or may be administered several times a day (e.g. the unit dose is a fraction of the desired daily dose). The unit dose may also be taken to indicate the total daily dose, which may be administered once per day or may be administered as a convenient fraction of such a dose (e.g. the unit dose is the total daily dose which may be given in fractional increments, such as, for example, one-half or one-third the dosage).

[0039] The term "sialorrhea" as used herein shall mean hypersalivation or excessive salivation or excessive saliva that may pool in the mouth and/or leak out. Sialorrhea is also known as drivel ing, ptalism, drooling or slobbering. Hypersalivation is generally caused by excess production of saliva, inability to retain saliva within the mouth, problems with swallowing or combinations thereof. In addition, the underlying etiology of sialorrhea may be, but not limited to, drug-induced or disease-induced.

[0040] Persistent or excessive drooling beyond the age of three years is considered abnormal. Such drooling may be found in individuals with neurological dysfunction or motor deficits (e.g., cerebral palsy, peripheral neuromuscular disease, facial paralysis, and mental
retardation) and other conditions such as esophageal cancer or as a side effect from a drug. Drooling causes impairment of speech, feeding and swallowing problems, upper respiratory congestion, and choking upon aspiration. Control of drooling is important in preventing choking and gagging in persons with posterior drooling. Sialorrhea may cause a range of physical and psychosocial complications, including perioral chapping, dehydration, odor, and social stigmatization, that can be devastating for patients and their families.


[0042] Clozapine is an antipsychotic medication used in the treatment of schizophrenia. Clozapine works well against positive (e.g. delusions, hallucinations) and negative (e.g. emotional and social withdrawal) symptoms of schizophrenia. It has no dyscognitive effect often seen with other psychoactive drugs and is even able to increase the capabilities of the patient to react to this environment and thereby fosters social rehabilitation.

[0043] Clozapine works by blocking receptors in the brain for several neurotransmitters including dopamine type 4 receptors, serotonin type 2 receptors, norepinephrine receptors, acetylcholine receptors and histamine receptors. Unlike traditional anti-psychotic agents, clozapine only weakly blocks dopamine type 2 receptors.

[0044] The use of clozapine is associated with a fair number of side effects, many minor though some serious and potentially fatal: the more common include constipation, drooling, muscle stiffness, sedation, tremors, orthostasis, hyperglycemia, and weight gain. The risks of extrapyramidal symptoms such as tardive dyskinesia are much less with clozapine when compared to the typical antipsychotics; this may be due to clozapine's anticholinergic effects.

[0045] Clozapine also carries a high potential for seizures, myocarditis, and other adverse cardiovascular and respiratory effects. Lowering of the seizure threshold may be dose related and slow initial titration of dose may decrease the risk for precipitating seizures. Slow titration of dosing may also decrease the risk for orthostatic hypotension and other adverse cardiovascular side effects.

[0046] Excessive salivation and sedation are the two most common side effects of clozapine. According to a recent, large, carefully controlled study, clozapine-induced sialorrhea ("CIS") continues to be the most common side effect (48%) associated with
clozapine treatment. CIS is often stigmatizing, functionally disabling, and may lead to medication discontinuation. In some cases, CIS may pose a major hurdle in the rehabilitation process of an otherwise clinically clozapine-responsive patient.

[0047] Bupropion as used herein is an atypical antidepressant that acts as a norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist. Bupropion belongs to the chemical class of aminoketones and is similar in structure to the stimulant cathinone, to the anorectic diethylpropion, and to phenethylamines in general. Bupropion lowers seizure threshold and increases the potential to have seizures.

[0048] In certain embodiments of the present application, methods of treating sialorrhea in a patient comprising administering a dopamine reuptake inhibitor or a pharmaceutically acceptable salt thereof to said patient are provided. Exemplary dopamine reuptake inhibitors include, but are not limited to, bupropion, bupropion metabolites, bupropion derivatives, bupropion isomers, triple monoamine reuptake inhibitor NS 2330, aminapine, benzatropine, dexamphetamine, esketamine, etybenzatropine, fencamfamine, fencamine, ketamine, lefetamine, medifoxamine, mesocarb, methylphenidate, nefopam, nomifensine, pipradrol, prolintane, pyrovalerone, tiletamine, tripeleennamine and combinations thereof.

[0049] In various embodiments of the invention, methods of treating CIS in a patient comprising administering bupropion, a bupropion metabolite, a bupropion derivative or a pharmaceutically acceptable salt thereof to said patient are provided.

[0050] In one embodiment, methods of treating sialorrhea by administering bupropion, bupropion derivatives and bupropion metabolites are disclosed. In certain embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable excipient and a therapeutically effective amount of bupropion, bupropion metabolite, bupropion derivative or a pharmaceutically acceptable salt is administered to a patient to treat sialorrhea.

[0051] In a preferred embodiment, bupropion metabolites comprise bupropion metabolite isomers. In certain embodiments, the bupropion metabolite isomers may have differential stereo-isomer activity.

[0052] In certain embodiments, exemplary bupropion metabolites include, but are not limited to, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[ (1,1 dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-
dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone.

[0053] In certain embodiments, exemplary pharmaceutical salts and solvates thereof include, but are not limited to, (+)-2- (tert-butylamino)-3'-chloropropiophenone hydrochloride, (+)- (2S, 3S)-2- (3-chlorophenyl)- 3,5,5-trimethyl-2-morpholinol, (R, R)-2 (3-chlorophenyl-2-hydroxy-3,5,5-trimethyl-morpholinol), (+/-) (2R*, 3R*)-2- (3-chlorophenyl)-3, 5,5-trimethyl-2-morpholinol hydrochloride, (+)- (2S, 3S)-2- (3-chlorophenyl)-3, 5,5-trimethyl-2-morpholinol hydrochloride and (2S,3S)-hydroxybupropion.

[0054] Embodiments are also directed to methods of treating drug-induced sialorrhea by administering bupropion, a bupropion metabolite or a pharmaceutically acceptable salt thereof to a patient. In certain embodiments, the bupropion, metabolite thereof or derivative thereof is administered in a therapeutically effective amount. In certain embodiments, sialorrhea is induced by a drug, including, but not limited to, for example psychotropics, antipsychotics, mercury, iodide, copper, arsenic, bitters, carbidopa-levodopa, carbidopa, levodopa, clozapine, clozapine metabolites and clozapine derivatives. In yet another embodiment, sialorrhea is induced by a drug including, but not limited to, for example, dopamine agonists, antipsychotic agents, acetylcholine esterase inhibitors, NMDA receptor antagonists, benzodiazepines, triptans, ethionamide, cholinomimetics and indirect cholinergic agonists, yohimbine, trazodone, organophosphates and combinations thereof.

[0055] In certain embodiments, exemplary dopamine agonists include, but are not limited to levodopa, carbidopa, bromocriptine, cabergoline, pergolide, pramipexole, ropinirole, 3ρορφρη, rotigotine and combinations thereof.

[0056] In certain embodiments, exemplary antipsychotic agents include, but are not limited to, quetiapine fumarate, paliperidone, risperidone, fluspirilene, remoxipride and combinations thereof.

[0057] In certain embodiments, exemplary acetylcholine esterase inhibitors include, but are not limited to Aricept, galanthamine, THA and combinations thereof.

[0058] In certain embodiments, exemplary NMDA receptor antagonists include, but are not limited to ketamine, ketamine stereoisomers, PCP and combinations thereof.

[0059] In certain embodiments, exemplary benzodiazepines include, but are not limited to diazepam, clonazepam, midazolam and combinations thereof. In yet another embodiment, triptans include, but are not limited to, sumatriptan.
In a preferred embodiment, sialorrhea is induced by clozapine, clozapine metabolites and clozapine derivatives. In certain embodiments, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, bupropion metabolite and a pharmaceutically acceptable salt is administered to a patient that is taking clozapine to treat the clozapine-induced sialorrhea.

Embodiments are also directed to methods of treating disease-associated sialorrhea by administering a therapeutically effective amount of bupropion and bupropion metabolites. In certain embodiments, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, bupropion metabolite and a pharmaceutically acceptable salt is administered to a patient that has disease-associated sialorrhea.

In certain embodiments, the sialorrhea may be caused by diseases selected from, but not limited to, retropharyngeal abscess, peritonsillar abscess, tonsillitis, mononucleosis, sore throat, stomatitis, chronic gastritis, pregnancy, maniacs, hydrophobia, Parkinson's disease, cerebral palsy, peripheral neuromuscular disease, facial paralysis, mental retardation and other conditions such as esophageal cancer.

In yet another embodiment, sialorrhea may be caused by diseases, including, but not limited to, amyotrophic lateral sclerosis (ALS), Huntington's Chorea, myasthenia gravis, Parkinson's disease, bulbar paralysis, bilateral facial nerve palsy, hypoglossal nerve palsy and combinations thereof.

In a preferred embodiment, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, bupropion metabolite or a pharmaceutically acceptable salt is administered to a patient that has Parkinson's disease to treat the Parkinson's-induced sialorrhea.

In yet another preferred embodiment, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, bupropion metabolite and a pharmaceutically acceptable salt is administered to a patient that has cerebral palsy to treat the cerebral palsy-induced sialorrhea.

In a preferred embodiment, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, a bupropion metabolite, a bupropion derivative and a pharmaceutically acceptable salt is administered to a patient has ALS disease to treat the ALS-induced sialorrhea.
[0067] In a preferred embodiment, a pharmaceutical composition comprising a therapeutically effective amount of bupropion, a bupropion metabolite, a bupropion derivative and a pharmaceutically acceptable salt is administered to a patient has Huntington's disease to treat the Huntington's-induced sialorrhea.

[0068] In certain embodiments, the pharmaceutical composition comprising bupropion, bupropion metabolites or pharmaceutically acceptable salts thereof may be an immediate release pharmaceutical formulation or a sustained release pharmaceutical formulation. Exemplary immediate release pharmaceutical formulations include wellbutrin. Exemplary sustained release pharmaceutical formulations include wellbutrin XL and wellbutrin SR.

[0069] In certain embodiments, a method of treating sialorrhea by administering therapeutically effective amount of bupropion is disclosed wherein the therapeutically effective amount is not 150 mg.

[0070] In certain embodiments, a method of treating sialorrhea by administering therapeutically effective amount of bupropion is disclosed wherein the therapeutically effective amount is from 1-145 mg, such as 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140 and 145 mg.

[0071] In certain embodiments, a method of treating sialorrhea by administering therapeutically effective amount of bupropion is disclosed wherein the therapeutically effective amount is from 1-150 mg, such as 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145 and 150 mg.

[0072] In certain embodiments, a method of treating sialorrhea by administering therapeutically effective amount of bupropion is disclosed wherein the therapeutically effective amount is from 155-250 mg, such as 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245 and 250 mg.

[0073] In certain embodiments, a method of treating sialorrhea by administering therapeutically effective amount of bupropion, wherein the therapeutically effective amount is selected from 1-145 mg and 155-250 mg is presented.

[0074] In certain embodiments, a method of treating sialorrhea by administering therapeutically effective amount of bupropion, wherein the therapeutically effective amount is selected from 1-150 mg and 155-250 mg is presented.
In certain embodiments a therapeutically effective amount of bupropion, metabolites or pharmaceutically acceptable salts thereof may be from about 10 to about 145 milligrams per day, from about 10 to about 125 milligrams per day, from about 25 to about 100 milligrams per day, from about 50 to about 140 milligrams per day, and from about 75 to about 125 milligrams per day. The total daily dose may be administered in one or more divided doses, including, for example, in a divided dose twice daily (e.g., every twelve hours).

In certain embodiments a therapeutically effective amount of bupropion, metabolites or pharmaceutically acceptable salts thereof may be from about 160 to about 230 milligrams per day, from about 160 to about 200 milligrams per day, from about 175 to about 225 milligrams per day, from about 200 to about 235 milligrams per day, and from about 185 to about 210 milligrams per day. The total daily dose may be administered in one or more divided doses, including, for example, in a divided dose twice daily (e.g., every twelve hours).

In certain embodiments, in order to minimize the risk of seizure, gradual escalation in dosage may be required, which may also be important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. In certain embodiment, the initial treatment for an adult target dose for may be 250 mg/day, given once daily in the morning. Dosing may begin at 125 mg/day given as a single daily dose in the morning. If the 125-mg initial dose is adequately tolerated, an increase to the 250-mg/day target dose, given as once daily, may be made.

In certain embodiments, the risk of dose-related side effects of bupropion when treating sialorrhea of any cause are minimized. Sialorrhea may be, for example, drug induced, Parkinson's disease related or cerebral palsy related. In certain embodiments, the lowest effective dose of bupropion that alleviates sialorrhea in a subject is identified. To identify the lowest effective dose, small incremental changes in the dose are made until the desired effect is reached. It is also possible that a response may be achieved at dosages lower than 150 mg per day while in other cases dosages significantly higher than 150 mg per day may be required. In this scenario dose increments of bupropion could be administered as
follows: 40, 80, 120, 160, 200, 240 and 280 mg in divided dosages per day or 45, 90, 135, 180, 225 and 270 mg in divided dosages per day.

[0079] In certain embodiments, the risk of seizures resulting form the combination of two drugs, each known to increase the risk of seizures, are minimized. In certain embodiments, the lowest effective dose of bupropion that alleviates clozapine-induced sialorrhea in a patient is identified. To identify the lowest effective dose, small incremental changes in the dose are made until the desired effect is reached. It is also possible that many patients may respond to dosages lower than 150 mg per day while other may require dosages significantly higher than 150 mg per day. In this scenario dose increments of bupropion could be administered as follows: 40, 80, 120, 160, 200, 240 and 280 mg in one or divided dosages per day or 45, 90, 135, 180, 225 and 270 mg in one or divided dosages per day.

[0080] In certain embodiments a therapeutically effective amount of bupropion, metabolites or pharmaceutically acceptable salts thereof may be from about 10 to about 1000 milligrams per day, from about 10 to about 500 milligrams per day, from about 25 to about 500 milligrams per day, from about 150 to about 450 milligrams per day, and from about 150 to about 300 milligrams per day. The total daily dose may be administered in one or more divided doses, including, for example, in a divided dose twice daily (e.g., every twelve hours).

[0081] In certain embodiments, in order to minimize the risk of seizure, gradual escalation in dosage may be required, which may also be important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. In certain embodiment, the initial treatment for an adult target dose for may be 300 mg/day, given once daily in the morning. Dosing with may begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target dose, given as a single or divided daily dose, may be made.

[0082] In other embodiments, the starting dose for sustained release bupropion may be 100 mg or 150 mg once daily. In certain embodiments the dose may be increased to about 100 to about 150 mg twice daily.
[0083] That there is no evidence in the literature to date to suggest that clozapine and bupropion potentiate each other's epileptogenicity. In fact there is no evidence that their epileptogenicity is additive. There is no report to date on occurrence of seizures in a patient treated with bupropion and clozapine.

[0084] In certain embodiments, if seizures are not of concern, a broader treatment strategy may be designed that starts at higher dose and uses larger increments. Such an escalation strategy may be administered as follows: 80, 160, 240 and 320 mg in one or divided dosages per day, 100, 200 and 300 mg in one or divided dosages per day or 90, 180, 270 and 360 mg in one or divided dosages per day.

[0085] In certain embodiments, increasing the dosage above 300 mg/day to, for example, 450 mg/day, given as a single or divided dose, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment.

[0086] In other embodiments, the starting dose for sustained release bupropion may be 50 mg or 130 mg once daily. In certain embodiments the dose may be increased to about 70 to about 140 mg twice daily.

[0087] In certain embodiments, bupropion, its metabolites or acceptable salts thereof are provided in a maintenance treatment regiment, wherein the patient requires several months or longer of sustained pharmacological therapy beyond response to an acute episode.

[0088] For example, in some aspects, the invention is directed to a pharmaceutical composition comprising a compound, as defined above, and a pharmaceutically acceptable carrier or diluent, or an effective amount of a pharmaceutical composition comprising a compound as defined above.

[0089] In certain embodiments, a pharmaceutical composition comprising a therapeutically effective amount of clozapine and bupropion are disclosed. In certain embodiments, a pharmaceutical composition comprising a therapeutically effective amount of clozapine, clozapine analogs, clozapine derivatives, clozapine isomers, bupropion and combinations thereof are disclosed. In certain embodiments, the composition may further include a pharmaceutical carrier or excipient.

[0090] In yet another embodiment, therapeutically effect amount of clozapine includes, but is not limited to, about 5 to 50 mgs, about 50 to 100 mgs and about 10 to 100 mgs.

[0091] In yet another embodiment, therapeutically effective amount of bupropion includes, but is not limited to, about 1 to 5 mgs, about 5 to 25 mgs, about 20 to 50 mgs and about 5 to 40 mgs.
[0092] In certain embodiments, the pharmaceutical composition comprises about 15 mgs of clozapine to about 5 mgs of bupropion.

[0093] In yet another embodiment, the pharmaceutical composition comprises about 30 mgs of clozapine to about 20 mgs of bupropion.

[0094] In another embodiment, the pharmaceutical composition comprises about 100 mgs of clozapine to about 30 mgs of bupropion.

[0095] In yet another embodiment, the pharmaceutical composition comprises about 100 mgs of clozapine to about 40 mgs of bupropion.

[0096] In another embodiment, methods of treating sialorrhea in a patient comprising administering a pharmaceutical excipient, a therapeutically effective amount of bupropion and a therapeutically effective amount of clozapine are disclosed.

[0097] In yet another embodiment, therapeutically effect amount of clozapine includes, but is not limited to, about 5 to 50 mgs, about 50 to 100 mgs and about 10 to 100 mgs.

[0098] In yet another embodiment, therapeutically effective amount of bupropion includes, but is not limited to, about 1 to 5 mgs, about 5 to 25 mgs, about 20 to 50 mgs and about 5 to 40 mgs.

[0099] In certain embodiments, the pharmaceutical composition comprises about 15 mgs of clozapine to about 5 mgs of bupropion.

[0100] In yet another embodiment, the pharmaceutical composition comprises about 30 mgs of clozapine to about 20 mgs of bupropion.

[0101] In another embodiment, the pharmaceutical composition comprises about 100 mgs of clozapine to about 30 mgs of bupropion.

[0102] In yet another embodiment, the pharmaceutical composition comprises about 100 mgs of clozapine to about 40 mgs of bupropion.

[0103] The compounds of the present invention can be administered in the conventional manner by any route where they are active. Administration can be systemic, topical, or oral. For example, administration can be, but is not limited to, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, oral, buccal, or ocular routes, or intravaginally, by inhalation, by depot injections, or by implants. In addition, the compounds of the present invention can be administered in an oral soluble film or fluid. Thus, modes of administration for the compounds of the present invention (either alone or in combination with other pharmaceuticals) can be, but are not limited to, sublingual, injectable (including short-acting, depot, implant and pellet forms injected subcutaneously or
intramuscularly), or by use of vaginal creams, suppositories, pessaries, vaginal rings, rectal suppositories, intrauterine devices, and transdermal forms such as patches and creams.

[00104] Specific modes of administration will depend on the indication. The selection of the specific route of administration and the dose regimen is to be adjusted or titrated by the clinician according to methods known to the clinician in order to obtain the optimal clinical response. The amount of compound to be administered is that amount which is therapeutically effective. The dosage to be administered will depend on the characteristics of the subject being treated, e.g., the particular animal, including humans, treated, age, weight, health, types of concurrent treatment, if any, and frequency of treatments, and can be easily determined by one of skill in the art (e.g., by the clinician). In certain embodiments, oral administration may be preferred.

[00105] Pharmaceutical formulations containing the compounds of the present invention and a suitable carrier can be solid dosage forms which include, but are not limited to, tablets, capsules, cachets, pellets, pills, powders and granules; topical dosage forms which include, but are not limited to, solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels and jellies, and foams; and parenteral dosage forms which include, but are not limited to, solutions, suspensions, emulsions, and dry powder; comprising an effective amount of a polymer or copolymer of the present invention. It is also known in the art that the active ingredients can be contained in such formulations with pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, Modem Pharmaceutics, Banker & Rhodes, Marcel Dekker, Inc. (1979); and Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, 6th Edition, MacMillan Publishing Co., New York (1980) can be consulted.

[00106] The compounds of the present invention can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. The compounds can be administered by continuous infusion subcutaneously over a period of about 15 minutes to about 24 hours. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.
[00107] For oral administration, the compounds can be formulated readily by combining these compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, elixir and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, but are not limited to, fillers such as sugars, including, but not limited to, lactose, sucrose, mannitol, and sorbitol; cellulose preparations such as, but not limited to, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as, but not limited to, the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00108] Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00109] Pharmaceutical preparations which can be used orally include, but are not limited to, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as, e.g., lactose, binders such as, e.g., starches, and/or lubricants such as, e.g., talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration.

[00110] For buccal administration, the compositions can take the form of, e.g., tablets, elixir or lozenges formulated in a conventional manner.

[00111] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g.,
dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00112] The compounds of the present invention can also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[00113] In addition to the formulations described previously, the compounds of the present invention can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection.

[00114] Depot injections can be administered at about 1 to about 6 months or longer intervals. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00115] In transdermal administration, the compounds of the present invention, for example, can be applied to a plaster, or can be applied by transdermal, therapeutic systems that are consequently supplied to the organism.

[00116] Pharmaceutical compositions of the compounds also can comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as, e.g., polyethylene glycols.

[00117] The compounds of the present invention can also be administered in combination with other active ingredients, such as, for example, adjuvants, or other compatible drugs or compounds where such combination is seen to be desirable or advantageous in achieving the desired effects of the methods described herein.

[00118] In some embodiments, the disintegrant component comprises one or more of croscarmellose sodium, carmelllose calcium, crospovidone, alginic acid, sodium alginate, potassium alginate, calcium alginate, an ion exchange resin, an effervescent system based on food acids and an alkaline carbonate component, clay, talc, starch, pregelatinized starch, sodium starch glycolate, cellulose floe, carboxymethylcellulose, hydroxypropylcellulose, calcium silicate, a metal carbonate, sodium bicarbonate, calcium citrate, or calcium phosphate.

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In some embodiments, the diluent component comprises one or more of mannitol, lactose, sucrose, maltodextrin, sorbitol, xylitol, powdered cellulose, microcrystalline cellulose, carboxymethylcellulose, carboxyethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose, starch, sodium starch glycinate, pregelatinized starch, a calcium phosphate, a metal carbonate, a metal oxide, or a metal aluminosilicate.

In some embodiments, the optional lubricant component, when present, comprises one or more of stearic acid, metallic stearate, sodium stearyl fumarate, fatty acid, fatty alcohol, fatty acid ester, glyceryl behenate, mineral oil, vegetable oil, paraffin, leucine, silica, silicic acid, talc, propylene glycol fatty acid ester, polyethoxylated castor oil, polyethylene glycol, polypropylene glycol, polyalkylene glycol, polyoxyethylene-glycerol fatty ester, polyoxyethylene fatty alcohol ether, polyethoxylated sterol, polyethoxylated castor oil, polyethoxylated vegetable oil, or sodium chloride.

As used herein, the term "alginic acid" refers to a naturally occurring hydrophilic colloidal polysaccharide obtained from the various species of seaweed, or synthetically modified polysaccharides thereof.

As used herein, the term "sodium alginate" refers to a sodium salt of alginic acid and can be formed by reaction of alginic acid with a sodium containing base such as sodium hydroxide or sodium carbonate. As used herein, the term "potassium alginate" refers to a potassium salt of alginic acid and can be formed by reaction of alginic acid with a potassium containing base such as potassium hydroxide or potassium carbonate. As used herein, the term "calcium alginate" refers to a calcium salt of alginic acid and can be formed by reaction of alginic acid with a calcium containing base such as calcium hydroxide or calcium carbonate. Suitable sodium alginates, calcium alginates, and potassium alginates include, but are not limited to, those described in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by reference in its entirety. Suitable sodium alginates, include, but are not limited to, Kelcosol (available from ISP), Kelfone LVCR and HVCR (available from ISP), Manucol (available from ISP), and Protanol (available from FMC Biopolymer).

As used herein, the term "calcium silicate" refers to a silicate salt of calcium.

As used herein, the term "calcium phosphate" refers to monobasic calcium phosphate, dibasic calcium phosphate or tribasic calcium phosphate.

Cellulose, cellulose floe, powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, carboxyethylcellulose, carboxymethylcellulose,
hydroxyethylcellulose, methylhydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate, ethylcellulose, methylcellulose, carboxymethylcellulose sodium, and carboxymethyl cellulose calcium include, but are not limited to, those described in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by reference in its entirety. As used herein, cellulose refers to natural cellulose. The term "cellulose" also refers to celluloses that have been modified with regard to molecular weight and/or branching, particularly to lower molecular weight. The term "cellulose" further refers to celluloses that have been chemically modified to attach chemical functionality such as carboxy, hydroxyl, hydroxyalkylene, or carboxyalkylene groups. As used herein, the term "carboxyalkylene" refers to a group of formula -alkylene-C(0)OH, or salt thereof. As used herein, the term "hydroxyalkylene" refers to a group of formula -alkylene-OH.

[00126] Suitable powdered celluloses for use in the invention include, but are not limited to Arbocel (available from JRS Pharma), Sanacel (available from CFF GmbH), and Solka-Floc (available from International Fiber Corp.).

[00127] Suitable microcrystalline celluloses include, but are not limited to, the Avicel pH series (available from FMC Biopolymer), Celex (available from ISP), Celphere (available from Asahi Kasei), Ceolus KG (available from Asahi Kasei), and Vivapur (available from JRS Pharma).

[00128] As used herein, the term "silicified microcrystalline cellulose" refers to a synergistic intimate physical mixture of silicon dioxide and microcrystalline cellulose. Suitable silicified microcrystalline celluloses include, but are not limited to, ProSolv (available from JRS Pharma).

[00129] As used herein, the term "carboxymethylcellulose sodium" refers to a cellulose ether with pendant groups of formula Na+ -0-C(0)-CH₂⁻, attached to the cellulose via an ether linkage. Suitable carboxymethylcellulose sodium polymers include, but are not limited to, Akucell (available from Akzo Nobel), Aquasorb (available from Hercules), Blanose (available from Hercules), Finnifix (available from Noviant), Nymel (available from Noviant), and Tylose CB (available from Clariant).

[00130] As used herein, the term "carboxymethylcellulose calcium" refers to a cellulose ether with a pendant groups of formula -CH₂⁻0-C(0)-0 · ½ Ca²⁺, attached to the cellulose via an ether linkage.
As used herein, the term "carboxymethylcellulose" refers to a cellulose ether with pendant carboxymethyl groups of formula \( \text{HO-C(O)-CH}_2^- \), attached to the cellulose via an ether linkage. Suitable carboxymethylcellulose calcium polymers include, but are not limited to, Nymel ZSC (available from Noviant).

As used herein, the term "carboxyethylcellulose" refers to a cellulose ether with pendant carboxymethyl groups of formula \( \text{HO-C(O)-CH}_2^-\text{CH}_2^- \), attached to the cellulose via an ether linkage.

As used herein, the term "hydroxyethylcellulose" refers to a cellulose ether with pendant hydroxyethyl groups of formula \( \text{HO-CH}_2^-\text{CH}_2^- \), attached to the cellulose via an ether linkage. Suitable hydroxyethylcelluloses include, but are not limited to, Cellosolve HEC (available from DOW), Natrosol (available from Hercules), and Tylose PHA (available from Clariant).

As used herein, the term "methylhydroxyethylcellulose" refers to a cellulose ether with pendant methoxyethyl groups of formula \( \text{CH}_3\text{-O-CH}_2^-\text{CH}_2^- \), attached to the cellulose via an ether linkage. Suitable methylhydroxyethylcelluloses include, but are not limited to, the Culminal MHEC series (available from Hercules), and the Tylose series (available from Shin Etsu).

As used herein, the term "hydroxypropylcellulose", or "hypomellose", refers a cellulose that has pendant hydroxypropoxy groups, and includes both high- and low-substituted hydroxypropylcellulose. In some embodiments, the hydroxypropylcellulose has about 5% to about 25% hydroxypropyl groups. Suitable hydroxypropylcelluloses include, but are not limited to, the Klucel series (available from Hercules), the Methocel series (available from Dow), the Nisso HPC series (available from Nisso), the Metolose series (available from Shin Etsu), and the LH series, including LHR-11, LH-21, LH-31, LH-20, LH-30, LH-22, and LH-32 (available from Shin Etsu).

As used herein, the term "methyl cellulose" refers to a cellulose that has pendant methoxy groups. Suitable methyl celluloses include, but are not limited to Culminal MC (available from Hercules).

As used herein, the term "ethyl cellulose" refers to a cellulose that has pendant ethoxy groups. Suitable ethyl celluloses include, but are not limited to Aqualon (available from Hercules).

As used herein, the term "carmellose calcium" refers to a crosslinked polymer of carboxymethylcellulose calcium.
[00139] As used herein, the term "crocarmellose sodium" refers to a crosslinked polymer of carboxymethylcellulose sodium.

[00140] As used herein, the term "crospovidone" refers to a crosslinked polymer of polyvinylpyrrolidone. Suitable crospovidone polymers include, but are not limited to Polyplasdone XL-10 (available from ISP) and Kollidon CL and CL-M (available from BASF).

[00141] As used herein, the term "crosslinked poly(acrylic acid)" refers to a polymer of acrylic acid which has been crosslinked. The crosslinked polymer may contain other monomers in addition to acrylic acid. Additionally, the pendant carboxy groups on the crosslinked polymer may be partially or completely neutralized to form a pharmaceutically acceptable salt of the polymer. In some embodiments, the crosslinked poly(acrylic acid) is neutralized by ammonia or sodium hydroxide. Suitable crosslinked poly(acrylic acid) polymers include, but are not limited to, the Carbopol series (available from Noveon).

[00142] As used herein, the term "an effervescent system based on food acids and an alkaline carbonate component" refers to a excipient combination of food acids and alkaline carbonates that releases carbon dioxide gas when administered. Suitable effervescent systems are those that those utilizing food acids (such as citric acid, tartaric acid, malic acid, fumaric acid, lactic acid, adipic acid, ascorbic acid, aspartic acid, erythorbic acid, glutamic acid, and succinic acid) and an alkaline carbonate component (such as sodium bicarbonate, calcium carbonate, magnesium carbonate, potassium carbonate, ammonium carbonate, etc.).

[00143] As used herein, the term "fatty acid", employed alone or in combination with other terms, refers to an aliphatic acid that is saturated or unsaturated. In some embodiments, the fatty acid in a mixture of different fatty acids. In some embodiments, the fatty acid has between about eight to about thirty carbons on average. In some embodiments, the fatty acid has about eight to about twenty-four carbons on average. In some embodiments, the fatty acid has about twelve to about eighteen carbons on average. Suitable fatty acids include, but are not limited to, stearic acid, lauric acid, myristic acid, erucic acid, palmitic acid, palmitoleic acid, capric acid, caprylic acid, oleic acid, linoleic acid, linolenic acid, hydroxystearic acid, 12-hydroxystearic acid, cetostearic acid, isostearic acid, sesquioleic acid, otherwise 9-octadecanoic acid, sesquinooctadecanoic acid, benhenic acid, isobehenic acid, and arachidonic acid, or mixtures thereof.

[00144] As used herein, the term "fatty acid ester" refers to a compound formed between a fatty acid and a hydroxyl containing compound. In some embodiments, the fatty acid ester is a sugar ester of fatty acid. In some embodiments, the fatty acid ester is a
glyceride of fatty acid. In some embodiments, the fatty acid ester is an ethoxylated fatty acid ester.

[00145] As used herein, the term "fatty alcohol", employed alone or in combination with other terms, refers to an aliphatic alcohol that is saturated or unsaturated. In some embodiments, the fatty alcohol in a mixture of different fatty alcohols. In some embodiments, the fatty alcohol has between about eight to about thirty carbons on average. In some embodiments, the fatty alcohol has about eight to about twenty-four carbons on average. In some embodiments, the fatty alcohol has about twelve to about eighteen carbons on average. Suitable fatty alcohols include, but are not limited to, stearyl alcohol, lauryl alcohol, palmityl alcohol, palmitolyl acid, cetyl alcohol, capryl alcohol, caprylyl alcohol, oleyl alcohol, linolenyl alcohol, arachidonic alcohol, behenyl alcohol, isobehenyl alcohol, selachyl alcohol, chimyl alcohol, and linoleyl alcohol, or mixtures thereof.

[00146] As used herein, the term "ion-exchange resin" refers to an ion-exchange resin that is pharmaceutically acceptable and that can be weakly acidic, weakly basic, strongly acidic or strongly basic. Suitable ion-exchange resins include, but are not limited to Amberlite™ IRP64, IRP88 and IRP69 (available from Rohm and Haas) and Duolite™ API 43 (available from Rohm and Haas). In some embodiments, the ion-exchange resin is a crosslinked polymer resin comprising acrylic acid, methacrylic acid, or polystyrene sulfonate, or salts thereof. In some embodiments, the ion-exchange resin is polacrilin resin, polacrilin potassium resin, or cholestyramine resin.

[00147] Suitable mannitols include, but are not limited to, PharmMannidex (available from Cargill), Pearlitol (available from Roquette), and Mannogem (available from SPI Polyols).

[00148] As used herein, the term "metal aluminosilicate" refers to any metal salt of an aluminosilicate, including, but not limited to, magnesium aluminometasilicate. Suitable magnesium aluminosilicates include, but are not limited to Neusilin (available from Fuji Chemical), Pharmsorb (available from Engelhard), and Veegum (available from R.T. Vanderbilt Co., Inc.). In some embodiments, the metal aluminosilicate is bentonite.

[00149] As used herein, the term "metal carbonate" refers to any metallic carbonate, including, but not limited to sodium carbonate, calcium carbonate, and magnesium carbonate, and zinc carbonate.

[00150] As used herein, the term "metal oxide" refers to any metallic oxide, including, but not limited to, calcium oxide or magnesium oxide.
[00151] As used herein, the term "metallic stearate" refers to a metal salt of stearic acid. In some embodiments, the metallic stearate is calcium stearate, zinc stearate, or magnesium stearate. In some embodiments, the metallic stearate is magnesium stearate.

[00152] As used herein, the term "mineral oil" refers to both unrefined and refined (light) mineral oil. Suitable mineral oils include, but are not limited to, the Avatech™ grades (available from Avatar Corp.), Drakeol™ grades (available from Penreco), Sirius™ grades (available from Shell), and the Citation™ grades (available from Avater Corp.).

[00153] As used herein, the term "polyethoxylated castor oil", refers to a compound formed from the ethoxylation of castor oil, wherein at least one chain of polyethylene glycol is covalently bound to the castor oil. The castor oil may be hydrogenated or unhydrogenated. Synonyms for polyethoxylated castor oil include, but are not limited to polyoxyl castor oil, hydrogenated polyoxyl castor oil, microgolglyceroli ricinoleas, macrogolglyceroli hydroxystearas, polyoxyl 35 castor oil, and polyoxyl 40 hydrogenated castor oil. Suitable polyethoxylated castor oils include, but are not limited to, the Nikkol™ HCO series (available from Nikko Chemicals Co. Ltd.), such as Nikkol HCO-30, HC-40, HC-50, and HC-60 (polyethylene glycol-30 hydrogenated castor oil, polyethylene glycol-40 hydrogenated castor oil, polyethylene glycol-50 hydrogenated castor oil, and polyethylene glycol-60 hydrogenated castor oil, Emulphor™ EL-719 (castor oil 40 mole-ethoxylate, available from Stepan Products), the Cremophore™ series (available from BASF), which includes Cremophore RH40, RH60, and EL35 (polyethylene glycol-40 hydrogenated castor oil, polyethylene glycol-60 hydrogenated castor oil, and polyethylene glycol-35 hydrogenated castor oil, respectively), and the Emulgin® RO and HRE series (available from Cognis PharmaLine). Other suitable polyoxyethylene castor oil derivatives include those listed in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by reference in its entirety.

[00154] As used herein, the term "polyethoxylated sterol" refers to a compound, or mixture of compounds, derived from the ethoxylation of sterol molecule. Suitable polyethoxylated sterols include, but are not limited to, PEG-24 cholesterol ether, Solulan™ C-24 (available from Amerchol); PEG-30 cholesterol, Nikkol™ DHC (available from Nikko); Phytosterol, GENEROL™ series (available from Henkel); PEG-25 phyto sterol, Nikkol™ BPSH-25 (available from Nikko); PEG-5 soya sterol, Nikkol™ BPS-5 (available from Nikko); PEG-10 soya sterol, Nikkol™ BPS-10 (available from Nikko); PEG-20 soya sterol, Nikkol™ BPS-20 (available from Nikko); and PEG-30 soya sterol, Nikkol™ BPS-30 (available from Nikko). As used herein, the term "PEG" refers to polyethylene glycol.

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As used herein, the term "polyethoxylated vegetable oil" refers to a compound, or mixture of compounds, formed from ethoxylation of vegetable oil, wherein at least one chain of polyethylene glycol is covalently bound to the vegetable oil. In some embodiments, the fatty acids has between about twelve carbons to about eighteen carbons. In some embodiments, the amount of ethoxylation can vary from about 2 to about 200, about 5 to 100, about 10 to about 80, about 20 to about 60, or about 12 to about 18 of ethylene glycol repeat units. The vegetable oil may be hydrogenated or unhydrogenated. Suitable polyethoxylated vegetable oils, include but are not limited to, Cremaphor™ EL or RH series (available from BASF), Emulphor™ EL-719 (available from Stepan products), and Emulphor™ EL-620P (available from GAF).

As used herein, the term "polyethylene glycol" refers to a polymer containing ethylene glycol monomer units of formula \(-\text{OCH}_2\text{CH}_2\text{-}\). Suitable polyethylene glycols may have a free hydroxyl group at each end of the polymer molecule, or may have one or more hydroxyl groups etherified with a lower alkyl, e.g., a methyl group. Also suitable are derivatives of polyethylene glycols having esterifiable carboxy groups. Polyethylene glycols useful in the present invention can be polymers of any chain length or molecular weight, and can include branching. In some embodiments, the average molecular weight of the polyethylene glycol is from about 200 to about 9000. In some embodiments, the average molecular weight of the polyethylene glycol is from about 200 to about 5000. In some embodiments, the average molecular weight of the polyethylene glycol is from about 200 to about 900. In some embodiments, the average molecular weight of the polyethylene glycol is about 400. Suitable polyethylene glycols include, but are not limited to polyethylene glycol-200, polyethylene glycol-300, polyethylene glycol-400, polyethylene glycol-600, and polyethylene glycol-900. The number following the dash in the name refers to the average molecular weight of the polymer. In some embodiments, the polyethylene glycol is polyethylene glycol-400. Suitable polyethylene glycols include, but are not limited to the Carbowax™ and Carbowax™ Sentry series (available from Dow), the Lipoxol™ series (available from Brenntag), the Lutrol™ series (available from BASF), and the Pluricol™ series (available from BASF).

As used herein, the term "polyoxyethylene-alkyl ether" refers to a monoalkyl or dialkylether of polyoxyethylene, or mixtures thereof. In some embodiments, the polyoxyethylene-alkyl ether is a polyoxyethylene fatty alcohol ether.

As used herein, the term "polyoxyethylene fatty alcohol ether" refers to an monoether or diether, or mixtures thereof, formed between polyethylene glycol and a fatty
alcohol. Fatty alcohols that are useful for deriving polyoxyethylene fatty alcohol ethers include, but are not limited to, those defined herein. In some embodiments, the polyoxyethylene portion of the molecule has about 2 to about 200 oxyethylene units. In some embodiments, the polyoxyethylene portion of the molecule has about 2 to about 100 oxyethylene units. In some embodiments, the polyoxyethylene portion of the molecule has about 4 to about 50 oxyethylene units. In some embodiments, the polyoxyethylene portion of the molecule has about 4 to about 30 oxyethylene units. In some embodiments, the polyoxyethylene fatty alcohol ether comprises ethoxylated stearyl alcohols, cetyl alcohols, and cetylstearyl alcohols (cetearyl alcohols). Suitable polyoxyethylene fatty alcohol ethers include, but are not limited to, the Brij™ series of surfactants (available from Uniqema), which includes Brij 30, 35, 52, 56, 58, 72, 76, 78, 93Veg, 97, 98, and 721, the Cremophor™ A series (available from BASF), which includes Cremophor A6, A20, and A25, the Emulgen™ series (available from Kao Corp.), which includes Emulgen 104P, 123P, 210P, 220, 320P, and 409P, the Ethosperse™ (available from Lonza), which includes Ethosperse 1A4, 1A12, TDAa6, S120, and G26, the Ethylan™ series (available from Brenntag), which includes Ethylan D252, 253, 254, 256, 257, 2512, and 2560, the Plurafac™ series (available from BASF), which includes Plurafac RA20, RA30, RA40, RA43, and RA340, the Ritolet™ and Ritox™ series (available from Croda), which includes Volpo N 10, N 20, N 20, C2, 20, CS20, L4, and L23, and the Texafor™ series, which includes Texafor A1P, AP, A6, A10, A14, A30, A45, and A60. Other suitable polyoxyethylene fatty alcohol ethers include, but are not limited to, polyethylene glycol (13)stearyl ether (steareth-13), polyethylene glycol (14)stearyl ether (steareth-14), polyethylene glycol (15)stearyl ether (steareth-15), polyethylene glycol (16)stearyl ether (steareth-16), polyethylene glycol (17)stearyl ether (steareth-17), polyethylene glycol (18)stearyl ether (steareth-18), polyethylene glycol (19)stearyl ether (steareth-19), polyethylene glycol (20)stearyl ether (steareth-20), polyethylene glycol (12)isostearyl ether (isosteareth-12), polyethylene glycol (13)isostearyl ether (isosteareth-13), polyethylene glycol (14)isostearyl ether (isosteareth-14), polyethylene glycol (15)isostearyl ether (isosteareth-15), polyethylene glycol (16)isostearyl ether (isosteareth-16), polyethylene glycol (17)isostearyl ether (isosteareth-17), polyethylene glycol (18)isostearyl ether (isosteareth-18), polyethylene glycol (19)isostearyl ether (isosteareth-19), polyethylene glycol (20)isostearyl ether (isosteareth-20), polyethylene glycol (13)cetyl ether (ceteth-13), polyethylene glycol (14)cetyl ether (ceteth-14), polyethylene glycol (15)cetyl ether (ceteth-15), polyethylene glycol (16)cetyl ether (ceteth-16), polyethylene glycol (17)cetyl ether
(ceteth-17), polyethylene glycol (18)cetyl ether (ceteth-18), polyethylene glycol (19)cetyl ether (ceteth-19), polyethylene glycol (20)cetyl ether (ceteth-20), polyethylene glycol (13)isocetyl ether (isoceteth-13), polyethylene glycol (14)isocetyl ether (isoceteth-14), polyethylene glycol (15)isocetyl ether (isoceteth-15), polyethylene glycol (16)isocetyl ether (isoceteth-16), polyethylene glycol (17)isocetyl ether (isoceteth-17), polyethylene glycol (18)isocetyl ether (isoceteth-18), polyethylene glycol (19)isocetyl ether (isoceteth-19), polyethylene glycol (20)isocetyl ether (isoceteth-20), polyethylene glycol (12)oleyl ether (oleth-12), polyethylene glycol (13)oleyl ether (oleth-13), polyethylene glycol (14)oleyl ether (oleth-14), polyethylene glycol (15)oleyl ether (oleth-15), polyethylene glycol (12)lauryl ether (laureth-12), polyethylene glycol (12)isolauryl ether (isolaureth-12), polyethylene glycol (13)cetylstearyl ether (ceteareth-13), polyethylene glycol (14)cetylstearyl ether (ceteareth-14), polyethylene glycol (15)cetylstearyl ether (ceteareth-15), polyethylene glycol (16)cetylstearyl ether (ceteareth-16), polyethylene glycol (17)cetylstearyl ether (ceteareth-17), polyethylene glycol (18)cetylstearyl ether (ceteareth-18), polyethylene glycol (19)cetylstearyl ether (ceteareth-19), and polyethylene glycol (20)cetylstearyl ether (ceteareth-20). The numbers following the "polyethylene glycol" term refer to the number of oxyethylene repeat units in the compound. Blends of polyoxyethylene fatty alcohol ethers with other materials are also useful in the invention. A non-limiting example of a suitable blend is Arlacel™ 165 or 165 VEG (available from Uniqema), a blend of glycerol monostearate with polyethylene glycol-100 stearate. Other suitable polyoxyethylene fatty alcohol ethers include those listed in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by reference in its entirety.

[00159] As used herein, the term "polyoxyethylene-glycerol fatty ester" refers to ethoxylated fatty acid ester of glycerine, or mixture thereof. In some embodiments, the polyoxyethylene portion of the molecule has about 2 to about 200 oxyethylene units. In some embodiments, the polyoxyethylene portion of the molecule has about 2 to about 100 oxyethylene units. In some embodiments, the polyoxyethylene portion of the molecule has about 4 to about 50 oxyethylene units. In some embodiments, the polyoxyethylene portion of the molecule has about 4 to about 30 oxyethylene units. Suitable polyoxyethylene-glycerol fatty esters include, but are not limited to, PEG-20 glyceryl laurate, Tagat™ L (Goldschmidt); PEG-30 glyceryl laurate, Tagat™ L2 (Goldschmidt); PEG-15 glyceryl laurate, Glycerox™ L series (Croda); PEG-40 glyceryl laurate, Glycerox™ L series (Croda); PEG-20 glyceryl stearate, Capmul™ EMG (ABITEC), Aldo MS-20 KFG (Lonza); PEG-20
glyceryl oleate, Tagat™ 0 (Goldschmidt); PEG-30 glyceryl oleate, Tagat™ 02 (Goldschmidt).

[00160] As used herein, the term "propylene glycol fatty acid ester" refers to an monoether or diester, or mixtures thereof, formed between propylene glycol or polypropylene glycol and a fatty acid. Fatty acids that are useful for deriving propylene glycol fatty alcohol ethers include, but are not limited to, those defined herein. In some embodiments, the monoester or diester is derived from propylene glycol. In some embodiments, the monoester or diester has about 1 to about 200 oxypropylene units. In some embodiments, the polypropylene glycol portion of the molecule has about 2 to about 100 oxypropylene units. In some embodiments, the monoester or diester has about 4 to about 50 oxypropylene units. Suitable propylene glycol fatty acid esters include, but are not limited to, propylene glycol laurates: Lauroglycol™ FCC and 90 (available from Gatofosse); propylene glycol caprylates: Capryol™ PGMC and 90 (available from Gatofosse); and propylene glycol dicaprylocaprate: Labrafac™ PG (available from Gatofosse).

[00161] Suitable sorbitols include, but are not limited to, PharmSorbidex E420 (available from Cargill), Liponic 70-NC and 76-NC (available from Lipo Chemical), Neosorb (available from Roquette), Partech SI (available from Merck), and Sorbogem (available from SPI Polyols).

[00162] Starch, sodium starch glycolate, and pregelatinized starch include, but are not limited to, those described in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by reference in its entirety.

[00163] As used herein, the term "starch" refers to any type of natural or modified starch including, but not limited to, maize starch (also known as corn starch or maydis amylum), potato starch (also known as solani amylum), rice starch (also known as oryzae amylum), wheat starch (also known as tritici amylum), and tapioca starch. The term "starch" also refers to starchy that have been modified with regard to molecular weight and branching. The term "starch" further refers to starches that have been chemically modified to attach chemical functionality such as carboxy, hydroxyl, hydroxyalkylene, or carboxyalkylene groups. As used herein, the term "carboxyalkylene" refers to a group of formula -alkylene-C(0)OH, or salt thereof. As used herein, the term "hydroxyalkylene" refers to a group of formula -alkylene-OH. Suitable sodium starch glycolates include, but are not limited to, Explotab (available from JRS Pharma), Glycolys (available from
Roquette), Primojel (available from DMV International), and Vivastar (available from JRS Pharma).

[00164] Suitable pregelatinized starches include, but are not limited to, Lycatab C and PGS (available from Roquette), Merigel (available from Brenntag), National 78-1551 (available from National Starch), Spress B820 (available from GPC), and Starch 1500 (available from Colorcon).

[00165] As used herein, the term "stearoyl macrogol glyceride" refers to a polyglycolized glyceride synthesized predominately from stearic acid or from compounds derived predominately from stearic acid, although other fatty acids or compounds derived from other fatty acids may used in the synthesis as well. Suitable stearoyl macrogol glycerides include, but are not limited to, Gelucire® 50/13 (available from Gattefosse).

[00166] As used herein, the term "vegetable oil" refers to naturally occurring or synthetic oils, which may be refined, fractionated or hydrogenated, including triglycerides. Suitable vegetable oils include, but are not limited to castor oil, hydrogenated castor oil, sesame oil, corn oil, peanut oil, olive oil, sunflower oil, safflower oil, soybean oil, benzyl benzoate, sesame oil, cottonseed oil, and palm oil. Other suitable vegetable oils include commercially available synthetic oils such as, but not limited to, Miglyol™ 810 and 812 (available from Dynamit Nobel Chicals, Sweden) Neobee™ M5 (available from Drew Chemical Corp.), Alofine™ (available from Jarchem Industries), the Lubritab™ series (available from JRS Pharma), the Sterotex™ (available from Abitec Corp.), Softisan™ 154 (available from Sasol), Croduret™ (available from Croda), Fancol™ (available from the Fanning Corp.), Cutina™ HR (available from Cognis), Simulsol™ (available from CJ Petrov), EmCon™ CO (available from Amisol Co.), Lipvol™ CO, SES, and HS-K (available from Lipo), and Sterotex™ HM (available from Abitec Corp.). Other suitable vegetable oils, including sesame, castor, corn, and cottonseed oils, include those listed in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by reference in its entirety.

[00167] In certain embodiments, bupropion may be administered in an orally disintegrating tablet that dissolves or disintegrates rapidly with saliva, thus eliminating the need for chewing the tablet, swallowing an intact tablet, or taking the tablet with liquids (e.g., water). The orally disintegrating tablet preferably has a disintegration time of five minutes or less (e.g., four minutes or less, three minutes or less, two minutes or less, or 1.5 minutes or less), more preferably one minute or less (e.g., 55 seconds or less, 50 seconds or less, 45 seconds or less, 40 seconds or less, or 35 seconds or less), and desirably 30 seconds or less.
(e.g., 25 seconds or less, 20 seconds or less, 15 seconds or less, 10 seconds or less, or 5 seconds or less).

[00168] Since the orally disintegrating tablet disintegrates or dissolves in the mouth, preferably the taste of the bupropion and other accessory ingredients is masked. Taste masking can be achieved by any suitable manner, including the addition of flavoring agents and/or sweeteners, wet granulation or roller compaction with other excipients to minimize the presented surface area of the bupropion, spray drying, sealing with a suitable coating material (e.g., hydroxypropyl methylcellulose, ethylcellulose, methacrylates, Kollicoat.TM., and polyvinylpyrrolidone), and encapsulation.

[00169] For example, the active ingredient (e.g., bupropion) can be microencapsulated in one or more acrylic polymers (e.g., Eudragit E, Eudragit L-55, Eudragit RL) or gelatin. Additionally, fine granules of the drug (e.g., bupropion) and disintegrant (e.g., low substituted hydroxypropyl cellulose) can be coated with a water insoluble polymer (e.g., ethylcellulose) to mask the taste of the drug.

[00170] Suitable flavoring agents include, for example, strawberry flavor, grape flavor, cherry flavor, cotton candy flavor, mint flavor, or other suitable flavor. The flavoring agent or mixtures thereof typically is present in an amount of about 0.0001 wt. % to about 5 wt. %.

[00171] Suitable sweeteners include, for example, sugars such as sucrose, lactose, and glucose, cyclamate and salts thereof, saccharin and salts thereof, ammonium glycyrrhizinate, and aspartame. The sweetener or mixtures thereof typically is present in an amount of about 0.001 wt. % to about 70 wt. %.

[00172] The orally disintegrating tablets can be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Remington: The Science and Practice of Pharmacy, 21st Edition. Philadelphia, Pa.: Lippincott Williams & Wilkins, 2005. Such methods include the step of bringing into association the active ingredient with a carrier (i.e., a pharmaceutically acceptable carrier) which constitutes one or more accessory ingredients. Such accessory ingredients include those conventional in the art, such as, fillers (e.g., polyhydric alcohols, such as mannitol, sorbitol, and xylitol, or mixtures thereof); binders (e.g., acacia, tragacanth, gelatin, sucrose, pre-gelatinized starch, starch, sodium alginate, methylcellulose, sodium carboxymethyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, and polyacrylamide); diluents; disintegrants; lubricants (e.g., talc, magnesium stearate, mineral oil, and mixtures thereof); colorants; flavoring agents; preservatives (e.g., alkyl hydroxybenzoates or salts thereof, such
as methyl, ethyl, propyl, and/or butyl hydroxybenzoates; sorbic acid or a salt thereof; benzoic acid or a salt thereof, and mixtures thereof); and wetting agents.

[00173] In particular, the orally disintegrating tablet can be prepared by processes, including, but not limited to, freeze-drying or lyophilization, tablet molding, direct compression, spray drying, sublimation, mass extrusion, and microencapsulation. Such processes are well known in the art (see, e.g., U.S. Pat. Nos. 5,178,878, 5,501,861, 5,587,172, 5,607,697, 5,616,344, and 5,622,719, 5,683,720, 5,720,974, 5,807,577, 5,837,285, 5,939,091, 6,036,974, 6,316,026, and 6,696,085; and Bhaskaran et al., Indian Pharmacist, 1(2): 9-12 (2002)).

[00174] Examples of orally disintegrating tablets include Zydis.TM. tablets (R. P. Scherer, Inc.) (see, e.g., Seager, J. Pharm. Pharmacol., 50: 375-382 (1998)), Orasolv.TM. and Durasolv.TM. (CIMA Labs, Inc.) (see, e.g., U.S. Pat. Nos. 5,178,878, 6,024,981, 6,221,392, and 6,365,182), FlashTab.TM. (Ethypharm), WOWTAB.TM. (Yamanouchi Pharma Technologies), Ziplets.TM. (Eurand), and Fast Melt.TM. (Elan Corp.).

[00175] Freeze-drying or lyophilization results in tablets that are highly porous with a high specific surface area. The tablets dissolve rapidly and demonstrate improved absorption and bioavailability. Methods of preparing orally disintegrating tablets by lyophilization are known in the art, such as those disclosed in U.S. Pat. Nos. 5,955,488, 6,063,802, and 6,010,719; Corveleyn et al., and Int. J. Pharm., 152: 215-225 (2000); and Jaccard et al., Ann. Pharm. Fr., 43(2): 123-131 (1985).

[00176] Molded tablets disintegrate rapidly and can offer a pleasant taste due to the inclusion of water soluble sugars. Methods of preparing orally disintegrating tablets by tablet molding are well known in the art. For example, one method involves moistening a powder blend comprising the drug with a hydroalcoholic solvent, pressing the resulting solution into a mold plate to form a wetted mass (compression molding), and removing the solvent by air drying. In another method, molded forms are prepared using a heat-molding process (see, e.g., U.S. Pat. No. 5,466,464). An additional method of tablet molding is no-vacuum lyophilization, which involves the evaporation of a solvent from a drug solution or suspension at standard pressure (see, e.g., U.S. Pat. No. 5,298,261).

[00177] Spray drying results in highly porous, fine powders, which can be formed into orally disintegrating tablets. Methods of preparing orally disintegrating tablets by spray drying are known in the art (see, e.g., U.S. Pat. Nos. 5,587,180, 5,595,761, 5,635,210, and 5,807,576). For example, a formulation containing the drug, a support agent for the matrix (e.g., hydrolyzed gelatin and unhydrolyzed gelatin), a bulking agent (e.g., mannitol), and a
disintegrant (e.g., sodium starch glycolate or crosscarmellose) can be spray dried to yield a porous powder. Disintegration and dissolution can be further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate) before spray drying.

[00178] Sublimation results in the presence of a porous structure in the tablet matrix. Methods of preparing orally disintegrating tablets by sublimation are known in the art (see, e.g., U.S. Pat. Nos. 3,885,023, 4,134,943, 5,720,974, and 5,762,961, and Koizumi et al., Int. J. Pharm., 152: 127-131 (1997)). As an example, volatile ingredients (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phtalic anhydride, urea, and urethane) can be used in the tableting process, wherein the volatile material is removed by sublimation and a porous matrix is left behind.

[00179] The technique of direct compression can be applied to orally disintegrating tablets if disintegrants and/or sugar-based excipients are included in the tableting process. Methods of preparing orally disintegrating tablets by direct compression are known in the art. Microcrystalline cellulose, cross-linked carboxymethyl cellulose sodium, cross-linked polyvinyl pyrrolidone, and low or partially substituted hydroxypropyl cellulose absorb water and swell due to capillary action, making them effective disintegrants in the preparation of orally disintegrating tablets (see, e.g., Bi et al., Chem. Pharm. Bull., 44(1): 2121-2127 (1996); and Watanbe et al., Biol. Pharm. Bull., 18(9): 1308-1310 (1995)). Agar powder also can be used as a disintegrant because the powder absorbs water and swells considerably without forming a gel at physiological temperatures (see, e.g., Ito et al., Chem. Pharm. Bull, 44(11): 2132-2136 (1996)). Sugar-based excipients, such as dextrose, fructose, isomalt, maltitok, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol, also can be used in the direct compression process to impart aqueous solubility and sweetness. Furthermore, the fast disintegration of tablets can be achieved by incorporating effervescent disintegrating agents, which generate gas.

[00180] Suitable effervescent disintegrating agents include agents that evolve gas by means of a chemical reaction that takes place upon exposure of the effervescent disintegrating agent to water and/or to saliva in the mouth. The reaction is most often a result of the reaction of a soluble acid source and an alkali monocarbonate or carbonate source, which produces carbon dioxide gas upon contact with water or saliva. The acid sources can be any that are safe for human consumption including citric acid, tartic acid, amalic acid, fumeric acid, adipic acid, and succinic acid. Carbonate sources include dry solid carbonate and bicarbonate salt, such as sodium bicarbonate, sodium carbonate, potassium bicarbonate,
potassium carbonate, and magnesium carbonate. Reactants that generate oxygen or other gases that are safe for human consumption also are suitable.

[00181] In another embodiment, the orally disintegrating tablet for oral administration in the methods of the present invention, preferably for buccal delivery systems, comprises an adhesive layer comprising a hydrophilic polymer with one surface adapted to contact a first tissue of the oral cavity and adhere thereto when wet and an opposing surface in contact with and adhering to an adjacent drug/enhancer layer comprising a permeation enhancer and the bupropion composition. The drug/enhancer layer contacts and is in drug transfer relationship with the buccal mucosa when the adhesive layer contacts and adheres to the first tissue, preferably the gingiva. Typically the hydrophilic polymer comprises compounds selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, ethylcellulose, carboxymethyl cellulose, dextran, guar-gum, polyvinyl pyrrolidone, pectins, starches, gelatin, casein, acrylic acid polymers, polymers of acrylic acid esters, acrylic acid copolymers, vinyl polymers, vinyl copolymers, polymers of vinyl alcohols, alkoxy polymers, polyethylene oxide polymers, polyethers, and mixtures thereof.

[00182] The adhesive layer may additionally contain one or more members including, but not limited to, fillers, tableting excipients, lubricants, flavors, or dyes. The drug/enhancer layer additionally may contain one or more members, such as tableting excipients, fillers, flavors, taste-masking agents, dyes, stabilizers, enzyme inhibitors, and lubricants.

[00183] In a further embodiment, the bupropion may be administered transdermally. For example, including a single layer drug-in-adhesive patch, a multi-layer drug-in-adhesive patch, a matrix patch, or a reservoir patch. Typically, transdermal patches incorporate at least one adhesive to adhere the patch to the patient. Adhesives can include acrylics, vinyl acetates, natural and synthetic rubbers, ethylene-vinyl acetate copolymers, polysiloxanes, polyacrylates, polyurethanes, plasticized polyether block amide copolymers, plasticized styrene-rubber block copolymers, and mixtures thereof.

[00184] In another embodiment, the method of the present invention includes at least one skin penetration enhancer (i.e., enhancer) to enhance penetration of transdermally-administered bupropion. Skin penetration enhancers can include, for example, fatty acids or salts thereof, fatty alcohols, branched aliphatic alcohols, fatty acid alkyl esters, fatty acid monoesters of sorbitol and glycerol, fatty acid esters with glycolic acid and lactic acid and salts thereof, fatty acid amides, alkylpyrrolidones, or mixtures thereof.
Various aspects of the present invention will be illustrated with reference to the following non-limiting examples.

EXAMPLES

EXAMPLE 1 - The patient is a 48 year old African American male with 10 years of education and a long history of psychiatric illness involving prolonged psychiatric hospitalizations. At the time of the clozapine initiation, the patient's clinical status was characterized by prominent psychotic symptoms, delusions, marked thought disorder, aggressive behavior, sexual assaults, and requirement of daily one to one monitoring. His medication regimen at the time of the initiation of the clozapine treatment is detailed in Table 1.
Table 1

Medication regimen at the time of clozapine initiation and time of the report

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Indication</th>
<th>Medication regimen at the time of clozapine initiation</th>
<th>Medication regimen at the time of the report submission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychotropic Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Psychosis</td>
<td>20 mg p.o. BID</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Psychosis</td>
<td>1200 m p.o./day</td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Agitation</td>
<td>0.5 mg p.o. at bed time</td>
<td></td>
</tr>
<tr>
<td>Benztropine</td>
<td>Extrapyramidal side effects</td>
<td>1mg p.o. TID</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Agitation</td>
<td>2 mg po q6hrs prn</td>
<td></td>
</tr>
<tr>
<td>Valproic acid extended release</td>
<td>Psychosis and agitation</td>
<td>1000 mg p.o. BID</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>Psychosis</td>
<td></td>
<td>625 mg po/d</td>
</tr>
<tr>
<td>Wellbutrin SL</td>
<td>Sialorrhea</td>
<td></td>
<td>150 mg po QAM</td>
</tr>
<tr>
<td><strong>Non-Psychotropic Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucophage</td>
<td>Prevention of metabolic syndrome</td>
<td></td>
<td>1500 mg po/d</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Prophylaxis of atherosclerotic heart disease</td>
<td>81 mg p.o. QAM</td>
<td>81 mg p.o. QAM</td>
</tr>
<tr>
<td>Docusate sodium</td>
<td>Constipation</td>
<td>100mg p.o. QAM</td>
<td>100mg p.o. QAM</td>
</tr>
<tr>
<td>Multivitamin</td>
<td>not specified</td>
<td>1 tab p.o. QAM</td>
<td>1 tab p.o. QAM</td>
</tr>
<tr>
<td>L-thyroxine</td>
<td>Hypothyroidism</td>
<td>.05 mg p.o. QAM</td>
<td>.05 mg p.o. QAM</td>
</tr>
<tr>
<td>Diltiazem extended release</td>
<td>Hypertension</td>
<td>120 mg p.o. BID</td>
<td>120 mg p.o. BID</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Hypertension</td>
<td>5 mg po QAM</td>
<td>5 mg po QAM</td>
</tr>
<tr>
<td>Milk of magnesia</td>
<td>Constipation</td>
<td>30 ml p.o.</td>
<td>30 ml p.o.</td>
</tr>
</tbody>
</table>

[00187] Over the subsequent weeks the patient's clozapine dose was gradually increased to a total of 625 mg po/d. By the end of the clozapine titration period the patient's clinical condition improved considerably allowing for most of his other psychotropic medications to be discontinued as detailed in Table 1. On his new medication regimen, the aggressive and assaultive behavior resolved, the severity of his psychotic symptoms decreased, his inappropriate sexual behavior markedly diminished, and he became much more responsive to verbal redirection. Sialorrhea became gradually noticeable and clearly bothersome when the patient reached a clozapine dose of 250-300 mg po/d. CIS worsened when the clozapine dose reached 450 mg po/d. The patient drooled profusely throughout the
day. The front of his shirt was always wet and malodorous, and saliva dripped on to the floor, his seat, and all his clothes. Palliative measures such as requiring the patient to wear a bib during the day were not effective in reducing the social stigma. Although he had significantly improved clinically, the patient could not be involved in the rehabilitation process due to the social effects of his hypersalivation.

[00188] The decision was made, therefore, to address the CIS pharmacologically. The patient was treated sequentially with several agents based on published reports. All four initial drugs (benztropine, trihexyphenidyl, scopolamine patch, sublingual ipatropium bromide) failed to improve the patient's CIS (see Table 2).
Table 2
Medication (administered to treat clozapine induced sialorrhea in this patient) names, dosages, duration, and response

<table>
<thead>
<tr>
<th>Attempt #</th>
<th>Drug</th>
<th>Dose</th>
<th>Duration in days</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benztropine</td>
<td>1 mg po BID</td>
<td>251</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 mg PO BID</td>
<td>92</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Transdermal scopolamine patch, apply to postauricular area</td>
<td>Twice a week</td>
<td>87</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrice a week</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Trihexyphenidyl</td>
<td>5 mg PO BID</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg PO TID</td>
<td>17</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Ipatropium bromide spray sublingual</td>
<td>0.03% Two puffs TID</td>
<td>10</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.06% Two puffs TID</td>
<td>62</td>
<td>Minimal</td>
</tr>
<tr>
<td>5</td>
<td>Oxybutynin extended release</td>
<td>5 mg PO once a day</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg PO BID</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg PO TID</td>
<td>28</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg PO BID</td>
<td>9</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Tolterodine tartrate long acting</td>
<td>2 mg PO once a day</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 mg PO once a day</td>
<td>22</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Bupropion</td>
<td>100 mg PO once a day</td>
<td>18</td>
<td>Some</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg extended release PO once a day</td>
<td>&gt;300</td>
<td>Marked</td>
</tr>
</tbody>
</table>

Subsequently, other pharmacological agents that result in a high incidence of dry mouth and could potentially ameliorate the patient's CIS were identified: oxybutynin, tolterodine and bupropion (see Table 3). Both oxybutynin and tolterodine have been administered in conjunction with clozapine for urinary incontinence, and both were well tolerated. However, neither oxybutynin nor tolterodine were effective in reducing the patient's CIS (see Table 2).
TABLE 3
Comparison of incidence rates of dry mouth induced by active medication and placebo in controlled trials

<table>
<thead>
<tr>
<th>Medication Name (active ingredient)</th>
<th>Rate of dry mouth (%) induced by active agent</th>
<th>Rate of dry mouth (%) induced by placebo</th>
<th>Ratio of rates of dry mouth (%) induced by active agent/placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ditropan XL (Ortho-McNeil 2008)</td>
<td>61</td>
<td>29</td>
<td>2.1</td>
</tr>
<tr>
<td>Detrol LA (Novartis 2008)</td>
<td>23</td>
<td>8</td>
<td>2.9</td>
</tr>
<tr>
<td>Wellbutrin (GlaxoSmithKline 2007a)</td>
<td>27.6</td>
<td>18.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Wellbutrin XL (GlaxoSmithKline 2007b)</td>
<td>26</td>
<td>15</td>
<td>1.7</td>
</tr>
</tbody>
</table>

[00190] Finally bupropion was added to the patient's regimen in an attempt to reduce CIS. Clozapine and bupropion are both known to lower the seizure threshold. Since the patient was receiving valproic acid for antipsychotic augmentation (see Table 1), and had a therapeutic drug level of valproic acid (75.6 mcg/ml), the treatment team felt comfortable initiating treatment with bupropion. The patient was started on bupropion 100 mg po/d. Within a few days there was a noticeable improvement in the day time CIS. After eighteen days the dose was increased to Wellbutrin SR 150 mg po QAM/day. On this regimen, the patient had minimal CIS. This decrease in CIS resulted in the patient having improved hygiene, reduced salivation onto clothes and floor, reduced malodorous scents, and dramatic reduction of social stigmatization.

[00191] The patient has received the combination of clozapine 625 mg po/d and Wellbutrin SR 150 mg po/day for over 300 days as of the writing if this report without a seizure episode or any other untoward event. Clozapine levels were tested once over the course of treatment and revealed high levels of clozapine (1270 ng/ml) and norclozapine (460 ng/ml).

[00192] This patient was treated with clozapine and developed CIS, which responded to the addition of bupropion after failing to respond to the sequential addition of four separate treatments for CIS (benztropine, trihexyphenidyl, scopolamine patch, and sublingual ipatropium bromide). It also failed to respond, to the sequential addition of oxybutynin and tolterodine both of which were known to result in high rates of dry mouth, but to our knowledge have not been previously prescribed for CIS. All six agents mentioned above
were prescribed in moderate dosages (Table 3) due to concerns that their combination with clozapine could result in complications from excessive cholinergic blockade.

[00193] Bupropion led to a dramatic reduction in CIS. Bupropion has been reported to have low cholinergic blocking potential suggesting that other non-cholinergic effects mediated the reduction in CIS. It is possible that bupropion-mediated dopamine reuptake inhibition may act to reduce hypersalivation as well as to normalize the swallowing reflex abnormalities noticed in hypodopaminergic conditions such as Parkinson's disease.

[00194] Embodiments of the present disclosure provide for the first report of methods of treating CIS with bupropion. The combination of clozapine with bupropion raised concerns regarding the possible emergence of seizures. Treating the patient concomitantly with an antiepileptic agent, and limiting the dose of bupropion to 150 mg orally per day may have helped mitigate this seizure risk. The striking improvement observed in this case in the absence of any adverse effects raises the possibility that bupropion may be a viable treatment option for CIS.
I. Claims

What is claimed is:

1. A method of treating sialorrhea in a patient comprising:

   administering a therapeutically effective amount of bupropion or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein said therapeutically effective amount of bupropion is in a pharmaceutical composition.

3. The method of claim 2, wherein said pharmaceutical composition further comprise a pharmaceutical excipient.

4. The method of claim 1, wherein said bupropion is selected from R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1-dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol)amino]-1-propanone.

5. The method of claim 1, wherein said pharmaceutically acceptable salt is selected from (+)-2- (tert-buty lamino)-3’-chloropropiophenone hydrochloride, (+)- (2S, 3S)-2- (3-chlorophenyl)- 3,5,5-trimethyl-2-morpholinol, (R, R)-2 (3-chlorophenyl-2-hydroxy-3,55,trimethyl-morphinol), (+/-) (2R*, 3R*)-2- (3-chlorophenyl)-3, 5,5-trimethyl-2-morpholinol hydrochloride, and (+)- (2S, 3S)-2- (3-chlorophenyl)-3, 5,5-trimethyl-2-morpholinol hydrochloride and (2S,3S)- hydroxybupropion.

6. The method of claim 1, wherein said sialorrhea is induced by a drug.

7. The method of claim 6, wherein said drug is clozapine, clozapine derivatives and clozapine metabolites.

8. The method of claim 1, wherein said sialorrhea is induced by a disease.
The method of claim 8, wherein said disease is selected from retropharyngeal abscess, peritonsillar abscess, tonsillitis, Mononucleosis, sore throat, stomatitis, chronic gastritis, pregnancy, maniacs, hydrophobia, Parkinson's disease, cerebral palsy, peripheral neuromuscular disease, facial paralysis, mental retardation, esophageal cancer, amyotrophic lateral sclerosis, Huntington's Chorea, myasthenia gravis, Parkinson's disease, bulbar paralysis, bilateral facial nerve palsy, and hypoglossal nerve palsy.

The method of claim 8, wherein said disease is selected from Parkinson's disease and cerebral palsy.

The method of claim 1, wherein said bupropion or pharmaceutically acceptable salts are administered orally, parenterally, or transdermally.

The method of claim 2, wherein said pharmaceutical composition is selected from a tablet, a capsule, a dragee, a lozenge, an elixir and a solution.

The method of claim 2, wherein said pharmaceutical composition is immediate release or sustained release.

The method of claim 1, wherein said therapeutically effective amount of bupropion is not 150 mg.

The method of claim 1, wherein said therapeutically effective amount of bupropion is from about 1 milligrams to about 145 milligrams.

The method of claim 1, wherein said therapeutically effective amount of bupropion is from about 155 milligrams to about 250 milligrams.

The method of claim 1, wherein said therapeutically effective amount of bupropion is about 100 milligrams.

The method of claim 1, wherein said therapeutically effective amount of bupropion is about 200 milligrams.
19. The method of claim 1, wherein said therapeutically effective amount of bupropion is about 250 milligrams.

20. The method of claim 1, wherein said therapeutically effective amount of bupropion is from about 75 milligrams to about 450 milligrams.

21. The method of claim 1, wherein said therapeutically effective amount of bupropion is from about 150 milligrams to about 300 milligrams.

22. The method of claim 1, wherein said therapeutically effective amount of bupropion is about 150 milligrams.

23. A pharmaceutical composition comprising:

   a therapeutically effective amount of bupropion, a therapeutically effective amount of clozapine and a pharmaceutical excipient.

24. The composition of claim 23, wherein the therapeutically effective amount of bupropion is about 5 to 450 mgs.

25. The composition of claim 23, wherein the therapeutically effective amount of clozapine is about 15 to 100 mgs.

26. A method of treating sialorrhea in a patient comprising:

   administering a pharmaceutical composition comprising a therapeutically effective amount of bupropion, a therapeutically effective amount of clozapine and a pharmaceutically acceptable excipient.

27. The method of claim 26, wherein the therapeutically effective amount of bupropion is about 5 to 450 mgs.

28. The method of claim 26, wherein the therapeutically effective amount of clozapine is about 15 to 100 mgs.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 33/02 (2010.01)
USPC - 514/649

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A01N 33/02 (2010.01)
USPC - 514/649

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/649; 276; 345; 565
(Text Search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, USOC, EPAB, JPAB); Google Scholar and PubMed
Search Term: sialorrhea, hypersalivS, excessive, salivaS, bupropion, wellbutrin, dry mouth, dopamine reuptake, Shupropion, clozapine, dopamine, Hydroxybupropion, excipient, Parkinson's, tablet, immediate, sustained, release, drimeline, pytaiism, drooling, slobbering.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>STERN, R.G. et al. Clorazepine-Induced Sialorrhea Alleviated by Bupropion - A Case Report. Progress in Neuro-Psychopharmacology &amp; Biological Psychiatry. 01 October 2009, Vol 33(8), pages 1578-1580; pg 1578, col 1, para 3; col 2, para 2 to pg 1579, col 1, para 2; col 2, para 1.</td>
<td>1-3 and 6-28 **********</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
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  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search 16 November 2010 (16.11.2010)
Date of mailing of the international search report NOV 2010

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