TREATMENT OF MOTOR AND MOVEMENT DISORDER SIDE EFFECTS ASSOCIATED WITH PARKINSON'S DISEASE TREATMENTS

FIELD OF THE INVENTION

[0001] This invention relates generally to the administration of drugs having agonist activity at 5-HT_{1a} and/or 5-HT_{1b} receptors to patients in need thereof in order to prevent, attenuate and/or treat motor disorder side effects or movement disorders associated with drugs that increase the activity of the dopamine receptor, including dopamine agonists and partial agonists, whether acting directly or indirectly, as well as dopamine precursors, such as levodopa (L-DOPA). In particular, the invention relates to preventing and treating L-DOPA-induced dyskinesia (LID), and to preventing and treating Parkinson's disease, by administering eltoprazine, either alone or in combination with other compounds.

BACKGROUND OF THE INVENTION

[0002] Parkinson's disease is a chronic, progressive, hypokinetic neurodegenerative disorder characterized by impaired voluntary movement (See, Dale and Federman (eds.), WebMD *Scientific American Medicine,* NY: WebMD Corporation, Chapter 11, Section 15, pp. 1-21,2001; Lang and Lozano, N Engl J Med, 339: 1044, 1998; and Lang and Lozano, N Engl J Med, 339: 1130, 1998). Parkinson's disease occurs at least as a result of the death of dopamine-producing neurons in the substantia nigra of the midbrain. Dopamine is a neurotransmitter, or chemical messenger, that transports signals to the parts of the brain that control movement initiation and coordination. The loss of dopamine in the brain is associated with multiple primary symptoms including, for example, tremor of the hands, arms, legs, jaw, and face; rigidity or stiffness of the limbs and trunk; bradykinesia or slowness of movement; dyskinesia; and postural instability or impaired balance and coordination. The disease is also associated with dementia, sleep disturbances and cognitive confusion.

[0003] Parkinson's disease afflicts more than one million persons in the United States alone (Lang and Lozano, supra, 1998), with approximately 50,000 new cases diagnosed each year. It is generally a disease of late middle age, with typical onset occurring at about age 60.

About five percent of patients, however, have early-onset disease and are younger than 40 when symptoms begin.

[0004] Most reported treatment strategies for PD focus on symptom control through one or more of medication, surgery, and physical therapy. Administration of the dopamine precursor, L-DOPA (L-3,4-dihydroxyphenylalanine; levodopa) is reported as the most effective and most commonly used treatment for PD, as it reverses the motor deficits associated with PD more so than dopamine agonists (Goodman & Gillman's The Pharmacolgoical Basis of Therapeutics, 11th edition, L. Brunton editor, The McGraw Hill Company, 2006). Unfortunately, L-DOPA can cause debilitating side effects (LeWitt and Nyholm Neurology, 62:S9-S16, 2004), including severe nausea, vomiting, and psychosis. Moreover, with prolonged use, patients frequently experience other side effects such as dyskinesia, or abnormal, excessive movements in many patients, which can interfere with the management of PD (see, *e.g.*, Baldessarini RJ., *Am. J. Psychiatry*, 137: 1163-72 (1980); Samii *et al.*, *Lancet*, 363(9423): 1783-93(2004)).

[0005] Serotonin neurons are reported to play a role in the development of L-DOPA-induced dyskinesia (LID), and specifically, 5-HT_{1a} and 5-HT_{1b} receptors are thought to be involved (see, *e.g.*, Carta *et al.*, *Brain*, 130(7): 1819-33 (2007); and U.S. published application 2007/0249621). In rats, activation of 5-HT_{1a} and 5-HT_{1b} receptors, either separately, or in combination, was reported to reduce LID (Carta *et al.*, 2007). When administered together at certain low doses, 5-HT_{1a} and 5-HT_{1b} receptor agonists were stated to block LID in rats (Carta *et al.*, 2007). WO2010/063486 to Merz *et al.*, WO 2009/156380 to Bjorklund *et al.*; U.S. patent publication *2007/0249621* to Wolf *et. al.*; U.S. patent publication *2010/0179171* to Wolf *et. al.*; and European Patent Application No. 2193794 to Valastro *et al.* relate to the use of eltoprazine to treat LID in rats.

[0006] The binding profile of eltoprazine as reported by Sijbesma (Sijbesma, H. *et al.*, *European Journal of Pharmacology*, 187(2): 209-223, (1990)) shows the compound to be a selective 5-HT_1 ligand (selective with respect to all receptors other than 5-HT_1) and similar to serotonin in many respects except for a lower affinity for the 5-HT_{1d} receptor. The literature reports that eltoprazine acts as a mixed 5-HT_{1a}/5-HT_{1b} receptor agonist with roughly equipotent

affinity for each of these receptors (Schipper *et al.*, *Drug Metabol Drug Interact*, 8(1-2):85-114, (1990)). Eltoprazine has no relevant affinity for dopamine receptors. Among the 5-HT receptors, the 5-HT_{1b} receptor is located as an autoreceptor on axon terminals and is responsible for inhibiting neurotransmitter release, whereas it is also located postsynaptically as a heteroreceptor on axons and terminals of non-serotonergic neurons inhibiting their activity (Clark and Neumaier, *Psychopharmacol Bul*, 35(4):170-85, (2001)).

[0007] There exists a need to develop noninvasive treatments which can effectively prevent, attenuate, control, and treat the motor disorder side effects or movement disorders associated with drug treatments for PD. There is a need to prevent, attenuate, and treat L-DOPA-induced dyskinesia (LID), as well as to prevent, attenuate, and treat Parkinson's disease (PD). In particular, there is a need to develop strategies that target serotonin receptors, including 5-HT_{1a} and 5-HT_{1b} receptors, either in combination or separately, for the prevention, attenuation and treatment of movement disorders, such as L-DOPA-induced dyskinesia, associated with Parkinson's disease treatments. There is also a need to develop treatment strategies for controlling the symptoms of Parkinson's disease and other movement disorders and effective pharmaceutical compounds and dosages for treating these symptoms. In addition, there is a need for specific therapy regimens that maximize the efficacy, and reduce the side effects of existing medicines, for Parkinson's disease.

SUMMARY

[0008] This disclosure contemplates preventing, attenuating, and/or treating in patients (preferably humans) with PD, movement disorders, or motor disorder side effects associated with dopamine-related drugs, in addition to preventing, attenuating, and/or treating PD. The inventors have determined that certain doses of eltoprazine are efficacious in reducing LID in human patients, specifically when eltoprazine is administered to Parkinson's patients, at doses of 5 mg/day and 7.5 mg/day. Eltoprazine administration did not affect the efficacy of levodopa treatment, and was not associated with any serious adverse events.

[0009] The dopamine-related drugs encompassed by the disclosure include drugs that increase the activity of the dopamine receptor, including dopamine agonists and partial agonists, whether acting directly or indirectly, as well as dopamine precursors, such as L-DOPA. In

preferred embodiments, the disclosure encompasses preventing, attenuating, and/or treating motor disorder side effects, including but not limited to dyskinesia, that are associated with L-DOPA therapy in Parkinson's patients (L-DOPA-induced dyskinesia, LID). The methods of the disclosure comprise administering to a patient in need thereof a therapeutic dose of a compound having agonist activity at both the 5-HT_{1a} and 5-HT_{1b} receptors (eltoprazine or batoprazine as non-limiting examples), or two separate compounds having agonist activity, one targeting the 5-HT_{1a} receptor, and another compound targeting the 5-HT_{1b} receptor.

[0009a] Disclosed is a use of eltoprazine or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for treating a movement or motor disorder or side effect thereof associated with administration of levodopa, or a dopamine-related drug, in a patient having Parkinson's disease, wherein said medicament is for administration of a dose of eltoprazine or a pharmaceutically acceptable acid addition salt thereof to said patient in need of treatment to reduce said movement or motor disorder or side effect thereof, wherein said dose of eltoprazine comprises from about 0.25 mg/day to about 25 mg/day.

[0009b] In one aspect, there is provided use of eltoprazine or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for treating a movement or motor disorder or side effect thereof associated with administration of levodopa, or a dopamine-related drug, in a patient having Parkinson's disease, wherein said medicament is for administration of a dose of eltoprazine or a pharmaceutically acceptable acid addition salt thereof of from 2.5 mg/day to 10 mg/day to said patient in need of treatment to reduce said movement or motor disorder or side effect thereof; wherein said medicament comprising eltoprazine is for administration prior to, concurrently with, or subsequent to the administration of at least one additional active ingredient to treat, attenuate, or prevent said movement or motor disorder or side effect thereof associated with administration of levodopa or said dopamine-related drug to said patient, wherein the administration of the medicament comprising eltoprazine in combination with the at least one additional active ingredient results in a reduction of the dose of levodopa, or a dopamine-related drug needed to treat a movement or motor disorder or side effect thereof in the patient; and wherein said at least one additional active ingredient is selected from the group consisting of:

an (mTOR) complex 1 (mTORC1) inhibitor;
a 5-HT1a/2a/alpha-2 antagonist;
a 5-HT2a inverse agonist;
an adenosine A2a receptor antagonist;
an alpha-1 adrenoceptor antagonist;
an alpha-2 adrenergic receptor antagonist;
an AMPA antagonist;
an AMPA/kainite antagonist;
an anticonvulsant;
a beta-2 antagonist;
a CB agonist;
a D2/5-HT2A+ antagonist;
a dopaminergic stabilizer;
a dopaminergic function enhancer/glutamate release inhibitor;

a combinations of a MAO-B inhibitor and an acetylcholinesterase inhibitor;
an acetylcholinesterase inhibitor;
a cholinesterase inhibitor that inhibits both butyrylcholinesterase and acetylcholinesterase;
an H2 antagonist;
a kynurenic hydroxylase inhibitor;
an L-type Ca2+ antagonist or L-type calcium channel blocker;
an mGluR5 antagonist;
a monoamine reuptake inhibitor;
a mu opioid receptor agonist
a nicotinic acetylcholine receptor (nAChR) modulator;
a nicotinic antagonist;
a nitric oxide synthase inhibitor;
a nootropic compound;
an NR1A/2B NMDA antagonist;
an NR2B selective NMDA antagonist;
an omega-3 fatty acid;
an opiate antagonist;
an anticholinergic;
an SSRI (Selective Serotonin Reuptake Inhibitor);
a 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor;
a phosphodiesterase (PDE) inhibitor such as a phosphodiesterase 4 (PDE4) inhibitor or a phosphodiesterase 2 (PDE2) inhibitor; and
carbidopa.

[0009c] Disclosed is a use of a dose of eltoprazine or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for treating Parkinson's disease in a human subject in need thereof, wherein said medicament is to be administered with a dose of levodopa to said human subject, wherein said dose of eltoprazine or a pharmaceutically acceptable acid addition salt thereof comprises from 0.25 mg/day to 25 mg/day.

[0009d] In one aspect, there is provided use of eltoprazine or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for treating, attenuating, or preventing a movement or motor disorder, or side effect thereof associated with administration of levodopa (L-DOPA), a dopamine-related drug, or a non-L-DOPA-related drug to a patient having Parkinson's disease, wherein said medicament is for use in combination with deep brain stimulation and/or transcranial magnetic stimulation and wherein said eltoprazine or a pharmaceutically acceptable acid addition salt thereof is to be administered to the patient in a dose of from 2.5 mg/day to 10 mg/day.

The methods of the

disclosure also encompass preventing, attenuating, and/or treating PD in a patient in need thereof.

[0010] The disclosure encompasses many possible administration and dosage regimes, with administration strategies including, but not limited to, administration of the 5-$HT_{1a/1b}$ receptor agonist or partial agonist before or after initiation of L-DOPA or other dopamine-related drug administration, and administration of the 5-$HT_{1a/1b}$ receptor agonist or partial agonist before or after development of motor disorder side effects. Dosage strategies include therapeutic and sub-therapeutic dosages of L-DOPA or other dopamine-related drug. In certain embodiments, this disclosure encompasses a reduction in the dosage of L-DOPA or other dopamine-related drug after administration of the 5-$HT_{1a/1b}$ receptor agonist or partial agonist. In instances where eltoprazine is used as the 5-$HT_{1a/1b}$ receptor agonist, non-limiting examples of daily dosages include, 2.5 mg, 5.0 mg, 7.5 mg, and 10 mg as embodiments within the scope of the disclosure. Particularly preferred dosages of eltoprazine, in humans, are 5 mg/day and 7.5 mg/day. Administration schedules may also be altered to achieve a therapeutically effective concentration of compound to treat the disorder or symptoms described herein. In some embodiments, for example, the compound may be administered once per day, twice per day, thrice per day, 4 times per day, 5 times per day, 7 times per day or 10 times per day.

[0011] Kits comprising one or more of the following are also encompassed by the disclosure described herein: a compound having agonist activity at both the 5-HT_{1a} and 5-HT_{1b} receptors, or two separate compounds having agonist activity, one targeting the 5-HT_{1a} receptor, and another compound targeting the 5-HT_{1b} receptor, additional compounds, L-DOPA or other or other dopamine-related drug, and instructions for administration.

[0011a] Disclosed is a kit comprising therapeutically effective dosages of eltoprazine and levodopa, and further comprising instructions for use in administering said eltoprazine and said levodopa to a subject with Parkinson's disease.

Non-limiting examples of

such kits include a kit comprising eltoprazine, and a kit comprising eltoprazine, L-DOPA, a

DDCI inhibitor and/or COMT inhibitor, and optionally any other compound described herein, plus instructions for administration.

BRIEF DESCRIPTION OF THE FIGURES

[0012] **FIG. 1**: shows the efficacy of eltoprazine in treating levodopa-induced dyskinesia patients (per protocol population), measured using Clinical Dyskinesia Rating Scales (CDRS).

[0013] **FIG. 2**: shows that there is no significant change in the Unified Parkinson's Disease Rating Scales-III (UPDRS-III) of parkinsonian symptoms after eltoprazine administration, indicating that eltoprazine does not adversely interfere with the levodopa efficacy in Parkinson's patients.

DETAILED DESCRIPTION

[0014] This invention encompasses preventing, attenuating, and/or treating motor disorder side effects in a patient with PD, including but not limited to dyskinesia or other motor disorder side effects or movement disorders, that are associated with dopamine-related drugs, in addition to preventing, attenuating, and/or treating PD. The method of the invention comprises administering to a patient in need thereof a therapeutic dose of a compound having agonist activity at both the 5-HT_{1a} and 5-HT_{1b} receptors, or two separate compounds having agonist activity, one targeting the 5-HT_{1a} receptor, and another compound targeting the 5-HT_{1b} receptor. Optionally in combination with targeting the 5-HT_{1a} and 5-HT_{1b} receptors, the invention encompasses administering to the patient in need thereof a compound that targets the same, a similar, or a different drug pathway, one that is useful in treating L-DOPA-induced dyskinesia (LID) or other movement disorders or motor disorder side effects associated with dopamine-related drugs, one that is useful in treating PD, or one that is useful for treating both LID or other movement disorders, or motor disorder side effects associated with dopamine-related drugs and PD. This additional compound may also be useful such that the effective dose of L-DOPA or other dopamine-related drug that is necessary to treat PD is reduced. In some embodiments, the invention contemplates administering to the patient in need thereof L-DOPA, in addition to a compound that targets the same, a similar, or a different drug pathway, one that is useful in treating L-DOPA-induced dyskinesia (LID), one that is useful in treating PD, or one that is

useful for treating both LID or other movement disorders or motor disorder side effects associated with dopamine-related drugs and PD.

[0015] The dopamine-related drugs encompassed by the invention include drugs that increase the activity of the dopamine receptor, including dopamine agonists and partial agonists, whether acting directly or indirectly, as well as dopamine precursors, such as L-DOPA. In a preferred embodiment, the dopamine-related drug treatment is L-DOPA therapy.

[0016] In other embodiments, the dopamine-related drug may be a dopamine receptor agonist, including, but not limited to bromocriptine, pergolide, cabergoline, apomorphine, and lisuride, or a non-ergoline dopamine agonist, including, but not limited to ropinirole or pramipexole.

[0017] In yet other embodiments, the methods of the invention encompass preventing, attenuating, and/or treating any of the motor disorder side effects described herein, associated with a combination of dopamine-related drug treatments, such as a combination of a dopamine precursors, a combination of dopamine agonists or partial agonists, and a combination of one or more dopamine precursors and one or more dopamine agonists or partial agonists.

[0018] Dopamine precursors such as L-DOPA are often administered with a DOPA decarboxylase inhibitor (DDCI) (also known as aromatic L-amino acid decarboxylase inhibitors (AAADI)). Non-limiting examples of such compounds contemplated by the invention include benserazide (Madopar, Prolopa, Modopar, Madopark, Neodopasol, and EC-Doparyl); carbidopa (Lodosyn, Sinemet, Parcopa, and Atamet); and Methyldopa (Aldomet, Aldoril, Dopamet, and Dopegyt).

[0019] In addition to DDCIs, L-DOPA or other dopamine precursors are also often administered with compounds that inhibit the action of catechol-O-methyl transferase (COMT inhibitors). Non-limiting examples of COMT inhibitors contemplated by the invention are entacapone, tolcapone, and nitecapone.

[0020] The methods of the invention, therefore, encompass preventing, attenuating, and/or treating any of the motor disorder side effects described herein, associated with L-DOPA treatment or treatment with another dopamine-related drug, L-DOPA treatment or other

dopamine-related drug treatment in combination with DDCI (AAADI) treatment, L-DOPA treatment or other dopamine-related drug treatment in combination with COMT inhibitors, and L-DOPA treatment or other dopamine-related drug treatment in combination with DDCI (AAADAI) treatment and COMT inhibitors.

[0021] In one embodiment, the methods of the invention encompass preventing, attenuating, and/or treating any of the motor disorder side effects described herein, associated with administering the combination of carbidopa, levodopa, and entacapone. In one embodiment, the combination of carbidopa, levodopa, and entacapone is administered as Stalevo.

[0022] In another embodiment, the methods of the invention encompass preventing, attenuating, and/or treating PD itself, including the movement disorders associated with PD.

[0023] In preferred embodiments, the compound having agonist activity at both the 5-HT_{1a} and 5-HT_{1b} receptors is eltoprazine or a pharmaceutically acceptable salt thereof.

[0024] In one embodiment, this invention provides a method of prevention, attenuation, and/or treatment of motor disorder side effects, including but not limited to dyskinesia, that are associated with L-DOPA therapy or other dopamine-related drugs in Parkinson's patients comprising administering to a patient in need thereof a therapeutic dose of a compound or a combination of two or more different compounds that acts/act as an agonist or partial agonist at the 5-HT_{1a} receptor.

[0025] In another embodiment, this invention provides a method of prevention, attenuation, and/or treatment of motor disorder side effects, including but not limited to dyskinesia, that are associated with L-DOPA therapy or other dopamine-related drugs in Parkinson's patients comprising administering to a patient in need thereof a therapeutic dose of a compound or a combination of two or more different compounds that acts/act as an agonist or partial agonist at the 5-HT_{1b} receptor.

[0026] In another embodiment, this invention provides a method of prevention, attenuation, and/or treatment of motor disorder side effects, including but not limited to dyskinesia, that are associated with L-DOPA therapy or other dopamine-related drugs in

Parkinson's patients comprising administering to a patient in need thereof a therapeutic dose of a compound or a combination of two or more different compounds that acts/act as an agonist or partial agonist at both the 5-HT_{1a} and 5-HT_{1b} receptors. When a single compound is used, this compound may act as an agonist or partial agonist at both the 5-HT_{1a} and 5-HT_{1b} receptors. When two or more different compounds are used, certain compounds may act at solely on one receptor (5-HT_{1a} or 5-HT_{1b}) and certain compounds may act at both receptors. In one embodiment, each compound acts solely on a particular receptor (5-HT_{1a} or 5-HT_{1b}) with the combination of compounds used resulting in the activity of both receptors. In another embodiment, at least one compound acts on both receptors. In another embodiment, all compounds act on both receptors.

[0027] In one embodiment, this invention provides a method of prevention, attenuation, and/or treatment of motor disorder side effects, including but not limited to dyskinesia, that are associated with L-DOPA therapy or other dopamine-related drugs in Parkinson's patients comprising administering to a patient in need thereof a therapeutic dose of eltoprazine.

[0028] In one preferred embodiment, the invention provides a method of preventing, attenuating, and/or treating Parkinson's disease, comprising administering to a patient in need thereof a dopamine-related drug and most preferably, L-DOPA, in combination with a therapeutic dose of eltoprazine or a pharmaceutically acceptable acid addition salt thereof.

[0029] In some embodiments, the invention provides methods for treating one or more symptoms of Parkinson's disease. Examples of such symptoms include but are not limited to dyskinesia, hyperkinesia, speech changes, loss of facial expression, cognitive dysfunction, mood swings, emotionallability, euphoria, bipolar syndrome, anxiety, aphasia, dysphasia, or disturbances, dementia or confusion, depression, fear, anxiety, memory difficulties, slowed thinking, sexual dysfunction, fatigue, aching, and loss of energy.

[0030] For all the conditions described herein, one of ordinary skill in the art will appreciate how to determine the presence or absence of characteristic symptoms and also how to diagnose these conditions. A number of criteria for diagnosing disease are useful for characterizing these conditions such as for example, NINCDS-ADRDA criteria (McKhann *et al.*, 1984), the ICD-IO criteria (World Health Organization, 1992), and/or the DSM-IV criteria

(American Psychiatric Association, 1994). Other manuals useful in diagnosing the conditions described herein include for example, but are not limited to Oppenheimer's Diagnostic Neuropathology: A Practice Manual (Esiri and Perl, 2006, Hodder Amold, London.); Harrison's Principles of Internal Medicine (Ed. Kasper et al, 16th Ed. 2005 McGraw Hill, Columbus, Ohio); Goetz: Textbook of Clinical Neurology (Eds. Goetz, Pappert, 2nd Ed. 2003, W.B. Saunders, Philadelphia, Pa.). One of ordinary skill will be aware of other such manuals routinely used in the art to diagnose these conditions.

[0031] Eltoprazine (1-(2,3-dihydro-1, 4-benzodioxanyl-5-yl) piperazine) is particularly preferred for use with this invention, including pharmaceutically acceptable salts thereof, and preferably HCl. Another preferred compound that may be useful for this invention is batoprazine, (8-(1-piperazine)-2H-1-benzopyran-2-one). This invention also includes the use of prodrugs of the compounds of the formulas provided, specifically derivatives of the compounds of the formulas that are inactive but are converted to an active form in the body following administration.

[0032] Eltoprazine and processes for its synthesis are known in the art and is described in U.S. Pat. No. 4,833,142; U.S. Pat. No. 5,424,313; European Patent No. 189,612; and European Patent No. 138,280, each of which is incorporated herein by reference in its entirety. Eltoprazine is commercially available, for example, through Tocris Bioscience (Ellisville, Missouri).

[0033] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with one or more additional compound(s). The additional compound(s) may have actions that are similar to, synergistic to, or different than eltoprazine and/or its related compound(s). Non-limiting examples of additional compounds include (mTOR) complex 1 (mTORC1) inhibitors (*e.g.*, rapamycin), 5-HT_{1a} agonists (*e.g.*, buspirone, gepirone, tandospirone, flesinoxan, ziprasidone, and EMD128130 (sarizotan)), 5-$HT_{1a/2a/alpha\text{-}2}$ antagonists (*e.g.*, mirtazapine), 5-HT_{2a} inverse agonists (*e.g.*, ACP103 (pimvaserin), nelotanserin, eplivanserin, AC-90179 [2-(4-Methoxyphenyl)-N-(4-methyl-benzyl)-N-(1-methyl-piperidin-4-yl)-acetamide Hydrochloride]), adenosine A_{2a} receptor antagonists (*e.g.*, KW-6002 (istradefylline), SYN-115 (4-Hydroxy-N-[4-methoxy-7-(4-morpholinyl)-2-benzothiazolyl]-4-methyl-1-piperidinecarboxamide, Synosia Therapeutics), SCH420814 (preladenant), ZM-241,385 (4-(2-[7-

amino-2-(2-furyl) [1,2,4]-triazolo[2,3-a][1,3,5]triazin- 5-yl amino]ethyl) phenol), VER-7835 (2-amino-6-(furan-2-yl)-N-(thiophen-2-ylmethyl)-9H-purine-9- carboxamide), MSX-3 (3-(3-hydroxypropyl)-7-methyl-8-(m-methoxystyryl)-1-propargylxanthine), ST-1535 (2-butyl-9-methyl-8-(2H-1,2,3-triazol 2-yl)-9 H-purin-6-ylamine)), alpha(1) adrenoceptor antagonists (*e.g.*, HEAT (2-[[beta-(-4-hydroxyphenyl)ethyl]aminomethyl]-1-tetralone), alfuzosin, doxazosin, moxisylyte, prazosin, trimazosin), alpha-2 adrenergic receptor antagonists (*e.g.*, idazoxan, JP1730 (fipamezole), atipamezole, mianserin, phentolamine, tolazoline), AMPA antagonists (*e.g.*, E2007 (perampanel)), AMPA/kainite antagonists (*e.g.*, LY300164 [7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo(4,5H)-2,3-benzodiazepine]), anticonvulsants (*e.g.*, primidone, zonisamide, levetiracetam, mesuximide, eslicarbazepine acetate, pregabalin), beta-2 antagonists (*e.g.*, propranolol, alprenolol, carteolol, nadolol, sotalol, timolol), CB agonists (*e.g.*, nabilone and WIN55,212-2 ((R)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate)), D2 agonists (*e.g.*, cabergoline bromocriptine, quinpirole, terguride, lisuride), D2/5-HT2A + antagonists (*e.g.* clozapine and quetiapine), DA agonists (*e.g.* pergolide, bromocriptine, quinpirole, apomorphine), dopamine agonists (*e.g.*, pramipexole, ropinirole, cabergoline, rotigotine), dopaminergic stabilizers (*e.g.* ACR325, aripiprazole, pridopidine), non-ergoline dopamine agonists (*e.g.*, ropinirole, pramipexole), dopaminergic function enhancers/glutamate release inhibitors (*e.g.*, safinamide), monoamine oxidase (MAO) inhibitors, including MAO-A, and MAO-B inhibitors (*e.g.*, rasagiline, selegiline, safinamide, EVT-302 (Evotec AG)), combinations of MAO-B inhibitors and acetylcholinesterase inhibitors (*e.g.*, ladostigil (TV-3326)), acetylcholinesterase inhibitors (*e.g.*, doepezil), a cholinesterase inhibitor that inhibits both butyrylcholinesterase and acetylcholinesterase (*e.g.*, rivastigmine), H2 antagonists (*e.g.*, famotidine, cimetidine, burimamide, ranitidine, metiamide), kynurenic hydroxylase inhibitors (*e.g.* Ro 61-8048 (3,4-Dimethoxy-N-[4-(3-nitrophenyl)-2-thiazolyl]benzene sulfonamide), FCE 28833 [(R,S)-2-amino-4-oxo-4-(3',4'-dichlorophenyl) butanoic acid]), L-type Ca2+ antagonists including L-type calcium channel blockers (*e.g.*, isradipine, amlodipine, azelnidipine, cilnidipine, lacidipine, nimodipine, nilvadipine), topiramate, mGluR5 antagonists (*e.g.*, AFQ056, 6-methyl-2-(phenylethynyl)pyridine), monoamine reuptake inhibitors (*e.g.*, NS2330 (tesofensine), bicifadine, DOV-102,677 [(5R)-5-(3,4-dichlorophenyl)bicyclo[3.1.0]hexane]), mu opiod receptor agonists, nicotine (*e.g.*, NP002), nicotinic agonists or partial agonists (*e.g.*,

nicotine, acetylcholine, choline, epibatidine, lobeline, varenicline, sazetidine-A, DMXB-A (GTS-21, 3-2,4 dimethoxybenzylidene), SIB-1508Y (3-Ethynyl-5-[(2S)-1-methyl-2-pyrrolidinyl]pyridine)), nicotinic antagonists (*e.g.*, chlorisondamine, d-tubocurarine, mecamylamine, bupropion), nitric oxide synthase inhibitors (*e.g.*, 7-nitroindazole and NG-nitro-L-arginine), NMDA receptor antagonists (*e.g.*, remacemide, amantadine, memantine, rolicyclidine, ketamine, aptiganel), NMDA modulators (*e.g.*, Neu-120), NMDA/Sigma-1 antagonists (*e.g.*, dextromethorphan), nootropic compounds (*e.g.*, levitircetam), NR1A/2B NMDA antagonists (*e.g.*, Cl-1041 (5-[2-[4-(4-fluorobenzyl)piperidin-1-yl]ethylsulfinyl]-2,3-dihydro-1H-benzimidazol-2-one)), NR2B selective NMDA antagonists (*e.g.*, MK0657, CP-101,606 (traxoprodil), eliprodil, Ro 25-6981 ((±)-(R*,S*)-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidine propanol), EVT-101 (Evotec AG), EVT-103 (Evotec AG)), omega-3 fatty acids (*e.g.*, docosahexaenoic acid), opiate antagonists (*e.g.*, naltrexone), anticholinergics (*e.g.*, amantadine, ipratropium bromide, oxitropium bromide, tiotropium), selective kappa opioid agonists (*e.g.*, TRK820 (17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[*N*-methyl-*trans*-3-(3-furyl) acrylamido]morphinan hydrochloride) and U50,488 (2-(3,4-dichlorophenyl)-N-methyl-N-[(1R,2R)-2-pyrrolidin-1-ylcyclohexyl]acetamide)), SSRIs (*e.g.*, fluoxetine, paroxetine, sertraline, escitalopram, citalopram, fluvoxamine), AP09004, KW6500 (apomorphine), 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors (*e.g.*, SYN-118, Synosia Therapeutics), and phosphodiesterase (PDE) inhibitors, including at least PDE4 inhibitors (*e.g.*, ronomilast, roflumilast, mesembrine, rolipram, ibudilast, piclamilast, luteolin, cilomilast, tofimilast (9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9H-pyrazolo(3,4-c)-1,2,4-triazolo(4,3-a)pyridine), tipelukast, ibudilast, apremilast ((S)-N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl] acetamide, Celgene Corporation), CC-1088 (a thalidomide analog inhibitor of PDE4, Celgene Corporation), 8-biarylnaphthyridinones such as MK-0952 (Merck), DC-AT-46 (7-benzylamino-6-chloro-2 piperazino-4-pyrrolidino-pteridine), HT-0712 ((3R,5R)-5-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-(3-methylbenzyl)piperidin-2-one, Helicon Therapeutics, Inc.), MEM-1414 (Roche), MEM-1917 (Roche), MEM-1018 (Roche), MEM-1091 (Roche), DG071 (decode Genetics), and PDE2 inhibitors (*e.g.*, BAY 60-7550).

[0034] In one embodiment, eltoprazine and/or a related compound(s) is administered optionally in combination with one or more additional compound(s) listed above for prevention, attenuation, and/or treatment of dyskinesia or other motor disorder side effect that is associated with L-DOPA therapy or other dopamine-related drugs in Parkinson's patients. In another embodiment, eltoprazine and/or a related compound(s) is administered optionally in combination with one or more additional compound(s) listed above for prevention, attenuation, and/or treatment of PD.

[0035] In yet another embodiment, L-DOPA is administered to a PD patient in need thereof, and following this administration, by the methods described herein, eltoprazine and/or a related compound(s) is administered optionally in combination with one or more additional compound(s) listed above for prevention, attenuation, and/or treatment of dyskinesia that is associated with L-DOPA therapy. In yet another embodiment, L-DOPA is administered to a PD patient in need thereof following the administration of eltoprazine and/or a related compound(s) optionally in combination with one or more additional compound(s) listed above for prevention, attenuation, and/or treatment of dyskinesia that is associated with L-DOPA therapy.

[0036] In yet another embodiment, L-DOPA is administered to a PD patient in need thereof, and following this administration, by the methods described herein, eltoprazine and/or a related compound(s) is administered after the development of motor side effects, optionally in combination with one or more additional compound(s) listed above for prevention, attenuation, and/or treatment of dyskinesia that is associated with L-DOPA therapy.

[0037] In yet another embodiment, L-DOPA is administered to a PD patient in need thereof, and following this administration, by the methods described herein, eltoprazine and/or a related compound(s) is administered prior to the development of motor side effects, optionally in combination with one or more additional compound(s) listed above for prevention, attenuation, and/or treatment of dyskinesia that is associated with L-DOPA therapy.

[0038] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one anticonvulsant. In another embodiment, eltoprazine and/or a related compound(s) is administered in combination with primidone. In yet another

embodiment, eltoprazine and/or a related compound(s) is administered in combination with zonisamide.

[0039] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one mGluR5 antagonist. In another embodiment, eltoprazine and/or a related compound(s) is administered in combination with AFQ056.

[0040] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one L-type calcium channel blocker. In other embodiments, eltoprazine and/or a related compound(s) is administered in combination with isradipine, nimodapine, or nilvadipine.

[0041] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one NMDA receptor antagonist. In another embodiment, eltoprazine and/or a related compound(s) is administered in combination with remacemide. In yet another embodiment, eltoprazine and/or a related compound(s) is administered in combination with amantadine.

[0042] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one NMDA 2B receptor antagonist.

[0043] In another embodiment, eltoprazine and/or a related compound(s) is administered in combination with Ro 25-6981.

[0044] In yet another embodiment, eltoprazine and/or a related compound(s) is administered in combination with EVT-101 or EVT-103.

[0045] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one adenosine A_{2a} receptor antagonist. In another embodiment,

[0046] eltoprazine and/or a related compound(s) is administered in combination with KW-6002 (istradefylline). In a further embodiment, eltoprazine and/or a related compound(s) is administered in combination with SCH420814 (preladenant).

[0047] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one alpha-2 adrenergic receptor antagonist. In another embodiment, eltoprazine and/or a related compound(s) is administered in combination with JP1730 (fipamezole). In a further embodiment, eltoprazine and/or a related compound(s) is administered in combination with idazoxan. In yet another embodiment, eltoprazine and/or a related compound(s) is administered in combination with SYN-115 (4-Hydroxy-N-[4-methoxy-7-(4-morpholinyl)-2-benzothiazolyl]-4-methyl-1-piperidinecarboxamide, Synosia Therapeutics).

[0048] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor. In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with SYN-118, Synosia Therapeutics).

[0049] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one MAO-B inhibitor. In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with safinamide, rasagiline, selegiline, or ladostigil.

[0050] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one nicotinic acetylcholine receptor (nAChR) modulator. nAChR modulators include any compound that modulate the effect of the nAChR, including but not limited to nAChR selective or non-selective agonists, selective or non-selective partial agonists, competitive and non-competitive antagonists. In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with nicotine, acetylcholine, choline, epibatidine, lobeline, varenicline, or sazetidine-A.

[0051] In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with at least one phosphodiesterase (PDE) inhibitors, including at least PDE4 inhibitors and/or PDE2 inhibitors. In one embodiment, eltoprazine and/or a related compound(s) is administered in combination with ronomilast.

[0052] In one embodiment, the invention is not used for prevention, attenuation, and/or treatment of the associated cognitive impairment in PD. In another embodiment, the invention is

not used for prevention, attenuation, and/or treatment of any one or more of the following: Alzheimer's disease, Huntington's disease, Cushing's syndrome, Lewy body disease, multiple sclerosis, stroke, addictive disorders, pervasive development disorder, Fragile X syndrome, anxiety disorders, Prader-Willi Syndrome, schizophrenia, bipolar disorder, depressive disorders, vascular dementia, mild cognitive impairment, dementia, or delirium. In an alternative embodiment, the invention may be used for prevention, attenuation, and/or treatment of one or more of these disorders.

[0053] In one embodiment, the methods of the invention encompass preventing, attenuating, and/or treating a motor side effect associated with a dopamine-related drug for the treatment of PD, which is not L-DOPA.

[0054] In some embodiments, the invention encompasses preventing, attenuating, and/or treating in patients with PD, movement disorders, or motor disorder side effects associated with dopamine-related drugs, in addition to preventing, attenuating, and/or treating PD, by administering to a patient in need thereof a therapeutic dose of a compound having agonist activity at both the 5-HT_{1a} and 5-HT_{1b} receptors, or two separate compounds having agonist activity, one targeting the 5-HT_{1a} receptor, and another compound targeting the 5-HT_{1b} receptor, in combination with deep brain stimulation as performed in a surgical procedure, or in combination with magnetic brain stimulation, such as transcranial magnetic stimulation.

[0055] In one embodiment, the invention encompasses preventing, attenuating, and/or treating in patients with PD, movement disorders, or motor disorder side effects associated with dopamine-related drugs, in addition to preventing, attenuating, and/or treating PD, by administering to a patient in need thereof a therapeutic dose of eltoprazine in combination with deep brain stimulation and/or transcranial magnetic stimulation, and optionally in combination with any other compound described herein. Any order of treatment found to be beneficial is contemplated by the invention. For example, the deep brain stimulation and/or transcranial magnetic stimulation may precede the dopamine-related drug treatment, may follow the dopamine-related drug treatment, may precede the eltoprazine treatment, or may follow the eltoprazine treatment.

[0056] The doses of the compounds used in treating the disorders described herein in accordance with this invention will vary in the usual way with the seriousness of the disorder, the weight, and metabolic health of the individual in need of treatment. The preferred initial doses for the general patient population will be determined by routine dose-ranging studies, as are conducted, for example, during clinical trials. Therapeutically effective doses for individual patients may be determined, by titrating the amount of drug given to the individual to arrive at the desired therapeutic or prophylactic effect, while minimizing side effects.

[0057] Useful doses of eltoprazine are from about 0.25 to about 50 mg/day, from about 0.25 to about 30 mg/day, from about 0.25 to about 25 mg/day, from about 0.25 to about 20 mg/day, from about 0.25 to about 10 mg/day, from about 2.5 to about 10 mg/day, from about 2.5 to about 7.5 mg/day. In a preferred embodiment, the dose of eltoprazine and/or related compounds is from about 2.5 to about 10 mg/day. In another preferred embodiment, the dose of eltoprazine and/or related compounds is from about 2.5 to about 7.5 mg/day. In some embodiments, the daily dose of eltoprazine and/or related compounds is about 1 mg, 2 mg, 2.5 mg, 5 mg, 7 mg, 7.5 mg, 9 mg, 10 mg, 12 mg, 15 mg, 17 mg, 19 mg, 20 mg, or 25 mg/day. Administration schedules may also be altered to achieve a therapeutically effective concentration of compound to treat the disorder or symptoms described herein.

[0058] The inventors have discovered that particularly preferred and efficacious doses of eltoprazine for reducing and/or treating levodopa-induced dyskinesia in Parkinson's patients are 5 mg/day and 7.5 mg/day, as shown in Example 1, and Figure 1. In addition, the inventors have shown that administration of eltoprazine to Parkinson's patients already on levodopa treatment who then receive eltoprazine, do not show a reduction in the efficacy of levodopa therapy for treating PD, as shown in Example 1, and Figure 2. Further, eltoprazine was well-tolerated, and there were no serious adverse events from administration.

[0059] In some embodiments, eltoprazine and/or related compounds may be administered once per day, twice per day, thrice per day, 4 times per day, 5 times per day, 7 times per day or 10 times per day. In a preferred embodiment, eltoprazine is administered once per day. Often the dosage is divided equally throughout the day, however in some embodiments to treat certain disorders or symptoms, it may be useful to bias the dosage administration schedule so that most

of the daily treatment is administered at the beginning half of the day. In some embodiments, about 50%, 60%, 70% or 80% of the dosage is administered in the first half of the day. In other embodiments, it may be more appropriate to administer most of the dosage in the latter half of the day so that about 50%, 60% , 70% or 80% of the dosage is administered in the latter half of the day.

[0060] The 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists and, optionally, at least one additional compound, may be administered before, concurrently, or after administration of L-DOPA or other dopamine-related drug. In one embodiment, the 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists and, optionally, at least one additional compound, is administered before administration of L-DOPA or other dopamine-related drug. In one embodiment, after administration of the 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists and, optionally, at least one additional compound, the dose of L-DOPA or other dopamine-related drug is reduced.

[0061] The 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists may be administered before, concurrently, or after administration of at least one additional compound. In one embodiment, the 5-$HT_{1a/1b}$ receptor agonist partial agonist, or agonists are administered concurrently with one or more of the following additional compounds: anticonvulsants, mGluR5 antagonists, L-type calcium channel blockers, NMDA receptor antagonists, MAO-B inhibitors, HPPD inhibitors, adenosine A_{2a} receptor antagonists and/or alpha-2 adrenergic receptor antagonists.

[0062] The 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists and, optionally, at least one additional compound, may be administered before, concurrently, or after onset of symptoms. In one embodiment, the symptoms include a motor disorder side effect from use of L-DOPA or other dopamine-related drugs. In one embodiment, the 5-$HT_{1a/1b}$ receptor agonist and, optionally, at least one additional compound, is/are administered after the development of a motor disorder side effect. In one embodiment, the 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists and, optionally, at least one additional compound, is/are administered before the development of a motor disorder side effect.

[0063] Administration of the compounds of this invention may be by any method used for administering therapeutics, such as for example, oral, parenteral, intravenous, intramuscular, subcutaneous, rectal, or topical administration, such as through the use of a transdermal patch.

[0064] It will be appreciated by one of ordinary skill in the art that age of the patient with the conditions described herein may respond to treatment at different degrees depending on factors such as dosage or administration or the presence of other factors or co-morbid conditions. Therefore, one of ordinary skill in the art will appreciate that the methods described herein may be directed to a particular age group.

[0065] In addition to comprising the therapeutic compounds for use in this invention, especially eltoprazine [1-(2,3-dihyro-1, 4-benzodioxin-5-yl) piperazine] or pharmaceutically acceptable salts (preferably HCl in the case of eltoprazine) or pro-drug thereof, the pharmaceutical compositions for use with this invention may also comprise a pharmaceutically acceptable carrier. Such carriers may comprise additives, such as preservatives, excipients, fillers, wetting agents, binders, disintegrants, buffers may also be present in the compositions of the invention. Suitable additives may be, for example magnesium and calcium carbonates, carboxymethylcellulose, starches, sugars, gums, magnesium or calcium stearate, coloring or flavoring agents, and the like. There exists a wide variety of pharmaceutically acceptable additives for pharmaceutical dosage forms, and selection of appropriate additives is a routine matter for those skilled in art of pharmaceutical formulation.

[0066] The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions.

[0067] In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Unit dose forms for oral administration may be tablets, capsules, and the like, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; and carriers or fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine. Additives may include disintegrants, for example starch, polyvinylpyrrolidone, sodium starch

glycolate or microcrystalline cellulose; preservatives, and pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

[0068] In addition to unit dose forms, multi-dosage forms are also contemplated to be within the scope of the invention. Modified or controlled release dosage forms are contemplated for use in the invention, including, but not limited to sustained release dosage forms, extended release dosage forms, delayed release dosage forms, and pulsatile release dosage forms.

[0069] Suitable polymers for use in the controlled release formulations of the present invention include, but are not limited to uncrosslinked, linear polymers including cellulosic polymers, preferably hydroxyethyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose and hydroxypropyl cellulose, microcrystalline cellulose, methyl cellulose, and ethyl cellulose, and combinations thereof; covalently crosslinked insoluble polymers such as high molecular weight crosslinked homopolymers and copolymers of (meth) acrylic acid including carbopol resins, or mixtures of these uncrosslinked and covalently crosslinked polymers. Additionally suitable polymers include acrylic acid, methacrylic acid, methyl acrylate, ammonio methylacrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, vinyl polymers and copolymers such as polyvinyl pyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers, to name a few. Various combinations of two or more of the above polymers are also contemplated for use in the dosage forms of the invention.

[0070] Delayed release compositions may be prepared, for example, by employing slow release coatings, micro encapsulation, and/or slowly dissolving polymers.

[0071] The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, for example with an enteric coating.

[0072] Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable

vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel, and hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil or fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavoring or coloring agents.

[0073] For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved in water or saline for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, additives such as a local anesthetic, preservative and buffering agent can be dissolved in the vehicle. Suitable buffering agents are, for example, phosphate and citrate salts. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by conventional means, for example by exposure to radiation or ethylene oxide, before being suspended in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

[0074] The 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists and, optionally, at least one additional compound may be provided in a kit. In one embodiment, a kit may comprise at least one 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists, and at least one additional compound. In one embodiment, a kit may comprise at least one 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists, L-DOPA or other dopamine-related drug, and optionally at least one additional compound. In one embodiment, a kit may comprise eltoprazine, L-DOPA, and amantadine. In another embodiment, a kit may comprise eltoprazine, L-DOPA, and KW-6002 (istradefylline). In a further embodiment, a kit as in any one of the previously described may also include instructions for administration of the compounds. In one embodiment, the kit is intended for use by a subject having PD. In another embodiment, a kit may comprise at least one

5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists, at least one dopamine precursor, at least one DDCI, and instructions for administering the compounds. In another embodiment, a kit may comprise at least one 5-$HT_{1a/1b}$ receptor agonist, partial agonist, or agonists, at least one dopamine precursor, at least one DDCI, at least one COMT inhibitor, and instructions for administering the compounds.

[0075] All patents and patent publications referred to herein are hereby incorporated by reference.

[0076] Certain modifications and improvements will occur to those skilled in the art upon a reading of the foregoing description. It should be understood that all such modifications and improvements have been deleted herein for the sake of conciseness and readability but are properly within the scope of the following claims. It is understood that the following examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggestive to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

EXAMPLE 1

Treatment of motor disorder side effects associated with L-DOPA therapy using eltoprazine in human patients.

[0077] This example describes a multicenter, randomized, double-blind, placebo-controlled, dose finding study of oral eltoprazine in Parkinson's patients with L-DOPA induced dyskinesias, in a levodopa challenge-dose setting in Parkinson's Disease. A total of 22 patients participated in the study, out of which 18 patients fulfilled the protocol in terms of eligibility, interventions, and outcome assessment.

Inclusion Criteria:

[0078] Subjects had to meet all of the following criteria to be eligible for the study:

[0079] 1. Each patient had Parkinson's disease, defined according to the UK Brain Bank Criteria (see Hughes *et al.,* J Neurol Neurosurg Psychiatry, 1992. 55(3): p. 181-4; Lees *et*

al., Lancet, 2009. 373: p. 2055-66). Bradykinesia symptoms were combined with one of resting tremor, rigidity or postural imbalance.

[0080] 2. Each patient had been treated for at least 3 years with L-DOPA prior to this study.

[0081] 3. Each patient had significant dyskinesias after L-DOPA dosages according to clinical experience.

[0082] 4. Each patient had significant dyskinesias after the administration of a single challenge dose of L-DOPA using two dyskinesia rating scales. The screening test was performed with a challenge dose of 150% of the normal regular dose of L-DOPA. If no dyskinesias was present during the first challenge, the challenge was repeated on an alternate day (and) significant dyskinesias in a patient self-administered diary with 3 levels with 3 grades ("off," "on without dyskinesias," "on with hyperkinesias") after the challenge dose has been given. Patients were included if one of the two challenge tests were positive and diary was positive for dyskinesias. In addition to the observed types of dyskinesias (dystonia, hyperkinesias), a temporal patterns were described as "peak-of dose," "end-of-dose dyskinesias" and "bi-phasic dyskinesias." Quantification was made by "peak-of-dose" ratings and area-under-the-curve (AuC) of scores.

[0083] 5. Each patient was over 18 years of age.

[0084] 6. This inclusion criterion applied to females of child-bearing potential (not surgically sterilized and between menarche and 1 year postmenopausal) only. Each female patient tested negative for pregnancy at the time of enrollment based on a serum pregnancy test and agreed to use a reliable method of birth control during the study.

[0085] 7. Each patient signed informed consent.

[0086] 8. Each patient had to able to communicate effectively with the investigator and study coordinator.

Exclusion Criteria:

[0087] The presence of any of the following conditions excluded a subject from the study:

[0088] 1. Exclusion criteria for Parkinson's disease according to the UK Brain Bank Criteria for Parkinson's disease.

[0089] 2. Fulfillment of any other atypical parkinsonism diagnosis according to published criteria for multiple system atrophy (see Gilman, S., *et al.,* Neurology, 2008. 71(9): p. 670-6), progressive supranucelar paresis (see Litvan, I., *et al.,* Neurology, 1996. 47(1): p. 1-9), dementia with Lewy body (see McKeith, I.G., *et al.,* Neurology, 2005. 65(12): p. 1863-72), corticobasal gangliotic disease (see Litvan, I., *et al*., J Neuropathol Exp Neurol, 1996. 55(1): p. 97-105), and dementia with Parkinson's disease (see Emre, M., *et al.,* Mov Disord, 2007. 22(12): p. 1689-707; quiz 1837).

[0090] 3. Any suspected secondary parkinsonism; drug induced parkinsonism; toxininduced parkinsonism; trauma-induced parkinsonism; normal pressure hydrocephalus and vascular parkinsonism.

[0091] 4. Ongoing treatment with any selective serotonin re-uptake inhibitors (SSRI) or any combined serotonin-norepinephrine re-uptake inhibitors (SNRI) 4 weeks prior to the study.

[0092] 5. Ongoing treatment with anti-parkinsonism medications (Cabergoline; Duodopa infusion; ApoGo infusion; Amantadine; Memantine if used against dyskinesias), and other medication with the potential for drug-interactions.

[0093] 6. Significant depression defined as > 18 in the Montgomery Åsberg Depression Rating Scale combined with a clinical evaluation as to any clinical relevant depression.

[0094] 7. Pregnant or breast-feeding.

[0095] 8. Reduced kidney function; defined as a creatinine level > 120 μmol/L.

[0096] 9. Reduced liver function, defined as aspartate aminotransferase, ASAT > 1.0 μkat/L or alanine aminotransferase, ALAT > 1.0 μkat/L or glutamyl transpeptidase, GT > 1.6 μkat/L, or total bilirubin > 30 μmol/L, or alkaline phosphatase, ALP > 6.0 μkat/L.

[0097] 10. History of any other medical condition thought to interfere with the study or study medication (*i.e.*, recent myocardial infarction, uncontrolled diabetes, uncontrolled hypertension (systolic blood pressure > 180 mmHg), ongoing severe infection).

[0098] 11. Receipt of an investigational drug within 30 days or 5 half-lives of the drug, whichever is longer, prior to entering this study.

[0099] 12. Any known allergy to eltoprazine or the constituents of the study medication and the placebo capsules.

[0100] 13. Any indication that patients are unsuitable in any other way to participate in this study, in the opinion of the investigator.

[0101] This study also assessed the safety and tolerability of eltoprazine in adults with Parkinson's Disease using the following measures: a) population mean values for the change in dyskinesia ratings between the placebo and screening baseline values and any of the eltoprazine dosages used, calculated as the peak-effect on CDRS of any study medication; b) population mean values for the change in dyskinesia ratings between the placebo and screening baseline values and any of the eltoprazine dosages used, calculated as the AuC on Rush DRS of any study medication; c) any changes in the UPDRS-III total score; d) any change in the diary data set, between the baseline and placebo and any of the three study medication tests; e) any deterioration of the HADS scores after study medication compared with placebo; f) any development of depression over the course of the study period, determined by the Montgomery Åsberg Depression Rating Scale (MADRS) and clinical judgment; g) comparison between the effects on Rush Dyskinesia Rating Scale (DRS) and Clinical Dyskinesia Rating Scale (CDRS) Area under the Curve (AuC) and peak of dose effects for the three study medication dosages.

[0102] The study consisted of 7 visits, described below: a screening visit, five treatment visits, and one end-of-study visit.

[0103] *Screening Period (Visit 1)*

[0104] During the first visit, patients underwent screening for inclusion/exclusion criteria and safety assessments. Symptoms of parkinsonism, depression, and anxiety were assessed, and screening for significant L-DOPA dyskinesias were conducted using a challenge dose (150%) of L-DOPA. Subjects who were taking a prohibited medication were required to complete a washout period of appropriate length, as determined by the investigator. All patients received challenge doses (150% - up to a maximum of 250 mg) of L-DOPA at screening and at each treatment visit. L-DOPA was administered as Sinemet (L-DOPA combined with carbidopa in a fixed ratio of 4:1, unless a patient has a known allergy or intolerance to this drug). If a patient is intolerant to Sinemet, an equivalent dose of Madopar Quick could be used. There was an observation period of 3 hours (6 x 30 min, or 180 minutes) after dosing.

[0105] *Double-Blind Treatment Period (Visits 2-6)*

[0106] During each of five visits, and after a two-hour fast, each patient received a challenge dosage (150% - up to a maximum of 250 mg) of levodopa. Additionally, during each of the five treatment visits, patients were also treated with single dose treatments of oral capsules of three active study medication dosages (2.5 mg, 5 mg, or 7.5 mg of eltoprazine) or two placebo doses. The patients were periodically recorded for 180 minutes after treatment, and the videos were evaluated in a blinded manner.

[0107] Visit 2 occurred within 30 days of visit 1, and visits 3-6 followed one week apart from each other.

[0108] *Final Visit or Early Termination Visit (Visit 7)*

[0109] During the final visit or early termination visit, symptoms of parkinsonism, depression, anxiety, and L-DOPA dyskinesias were assessed, to capture any eltoprazine-related treatment effects on the degree of parkinsonism and any change in mood-related symptoms. Safety assessments were also conducted. A patient diary completed prior to and after the study period was used to evaluate any changes in perceived dyskinesias by the patients. A two-three day diary with 3 symptom lines – "off," "on (normal)," "on with dyskinesias" were filled out by each patient between the screening and enrollment visits and in between visits 2 through 6 to evaluate any changes in perceived dyskinesia by the patients.

[0110] The final visit, 7, was scheduled 4 days after visit 6. All study visits occurred within a ±5-day window of the time points noted above.

[0111] After screening, each patient participated in the study for approximately 6-10 weeks. The duration of the study was about 30 weeks. Safety evaluations were based on reports of adverse effects, concomitant therapy, clinical laboratory results, medical history, physical examination, and vital signs. Patient videos were used to assess efficacy. Rating scales include UPDRS, CDRS, and Rush DRS. In addition, patient diaries were used for self-assessment of dyskinesia.

Rating Scales

[0112] The term "Unified Parkinson's Disease Rating Scale - III" and "UPDRS-III" refer to a standardized tool used to measure Parkinson's Disease severity, as described by Fahn *et al.*, in Recent Developments in Parkinson's Disease, Fahn *et al.* (eds.) Plurham Park, N.J.: Macmillian Healthcare Information, 2:153-163,1987.

[0113] The term "Clinical Dyskinesia Rating Scale" and "CDRS" refer to a modified abnormal involuntary movement scale (AIMS) allowing for independent rating of limbs, trunk, head/neck and face rated during the UPDRS movements. This scale can simultaneously rate dystonia and dyskinesias, as described by Goetz *et al.*, in Movement Disorders, Vol. 9, No. 4, 1994, 390-394.

[0114] The term "Rush Dyskinesia Rating Scale" and "Rush DRS" refer to an observer-based rating scale based on fixed movements. The numerical parts of the Rush DRS are recorded separately from the descriptive parts, as described by Goetz *et al.*, in Movement Disorders, Vol. 9, No. 4, 1994, 390-394.

[0115] The term "Hospital Anxiety & Depression Scale" and "HADS" refer to rating scales commonly used by doctors to determine the levels of anxiety and depression that a patient is experiencing, as described by Zigmond *et al.*, in Acta Psychiatrica Scandinavica 67 (6): 361–370.

[0116] The term "Montgomery- Åsberg Depression Rating Scale" and "MADRS" refer to an observer based ten-item diagnostic questionnaire used by psychiatrists to measure the severity of depressive episodes in patients with mood disorders, as described by Montgomery *et al.*, in British Journal of Psychiatry 134 (4): 382–89.

[0117] Patients presenting clinically with motor disorder side effects associated with L-DOPA therapy, including dyskinesia, were evaluated using the United Parkinson's Disease Rating Scale III (Recent Developments in Parkinson's Disease, vol. 2, Fahn *et al.* editors, Macmillan Publishing Co. Inc, 1987), an art-recognized dyskinesia severity scale (Marconi *et al.*, *Mov Disord*, 9:2-12, (1994)). Briefly, the dyskinesia severity scale rates abnormal movements from 0 (none) to 4 (severe with markedly impaired function) in six different parts of the body (face, neck, and trunk, and four limbs).

Efficacy Assessments

Filming

[0118] Filming occurred 30 minutes prior to, and every 30 minutes up to 180 minutes after a challenge test of L-DOPA and study medication. Approximately 5 minutes of video filming were performed each time. The "UPRDS movements" in the UPDRS scale was performed (arms in different positions, repeated pronations-supinations of the wrists, finger tapping of opposing fingers, opening and closing of the fists, foot stamping, raising from the chair, walking with a turn and a balance test). Each patient also performed tasks for the "Dyskinesia Rating Scales." The same sequences were repeated prior to any challenge dose, and after every 30 minutes up to 180 minutes after the intake of the medications, for a total of 7 sequences. Each sequence was rated by two independent blinded raters using UPDRS, CDRS and Rush DRS. Video taped records of each sequence were assessed by separate individual qualified raters at both of the two clinical centers.

Patient diary

[0119] During screening, patients were asked to perform a self-administered rating of their dyskinesias by using a diary with 3 levels with 3 grades ("off," "on without hyperkinesias," and "on with hyperkinesias"). On the days following screening, the patients self rated their

symptoms over three days. A two day diary with 3-symptom lines ("off," "on," "on with dyskinesias") was filled out by patients between the screening and enrollment visits and in between the Visits 2 through 6 (one day before dosing and one day after dosing).

Efficacy Analyses

[0120] Analyses were done on both the intention-to-treat (ITT) and per protocol (PP) population, if applicable. The change between test sessions of the highest observed Unified Parkinson's Disease Rating Scale-III (UPDRS) within each session will be calculated between the randomised placebo test session and each active test session and will be analysed with Wilcoxon Signed Rank test on the ITT population.

[0121] The change in Mean AUC $_{0\text{-}3\ \text{hours}}$ of CDRS ratings will be analyzed between the randomised Placebo Test session and each active Test session with Wilcoxon Signed Rank test on the ITT population. Changes to all secondary variables between the randomized placebo test session and each active test session were analyzed using Wilcoxon Signed Rank test on both ITT- and PP-population.

Results

[0122] Statistical analyses demonstrated that eltoprazine administered to Parkinson's disease patients with levodopa-induced dyskinesia (LID), statistically significantly reduced LID at both the 5 mg dose ($p = 0.0007$) and the 7.5 mg dose ($p = 0.0467$), as compared to placebo, when measured by the CDRS scale (see Fig. 1). In addition, eltoprazine administration at these doses did not affect L-DOPA efficacy, as measured by the UPDRS score (see Fig. 2); both the 5 mg and 7.5 mg doses were statistically significant as compared to placebo). At the 5 mg dose, eltoprazine reduced LID in PD patients statistically significantly - as measured by the Rush Scale AUC.

[0123] Furthermore, eltoprazine was well tolerated in this study, as there were no serious adverse events.

[0124] All references, including patent applications and publications cited herein, are incorporated by reference in their entirety and for all purposes to the same extent as if each

individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

Claims

1. Use of eltoprazine or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for treating a movement or motor disorder or side effect thereof associated with administration of levodopa, or a dopamine-related drug, in a patient having Parkinson's disease, wherein said medicament is for administration of a dose of eltoprazine or a pharmaceutically acceptable acid addition salt thereof of from 2.5 mg/day to 10 mg/day to said patient in need of treatment to reduce said movement or motor disorder or side effect thereof; wherein said medicament comprising eltoprazine is for administration prior to, concurrently with, or subsequent to the administration of at least one additional active ingredient to treat, attenuate, or prevent said movement or motor disorder or side effect thereof associated with administration of levodopa or said dopamine-related drug to said patient, wherein the administration of the medicament comprising eltoprazine in combination with the at least one additional active ingredient results in a reduction of the dose of levodopa, or a dopamine-related drug needed to treat a movement or motor disorder or side effect thereof in the patient; and wherein said at least one additional active ingredient is selected from the group consisting of:

an (mTOR) complex 1 (mTORC1) inhibitor;

a 5-HT1a/2a/alpha-2 antagonist;

a 5-HT2a inverse agonist;

an adenosine A2a receptor antagonist;

an alpha-1 adrenoceptor antagonist;

an alpha-2 adrenergic receptor antagonist;

an AMPA antagonist;

an AMPA/kainite antagonist;

an anticonvulsant;

a beta-2 antagonist;

a CB agonist;

a D2/5-HT2A+ antagonist;

a dopaminergic stabilizer;

a dopaminergic function enhancer/glutamate release inhibitor;

a combinations of a MAO-B inhibitor and an acetylcholinesterase inhibitor;

an acetylcholinesterase inhibitor;

a cholinesterase inhibitor that inhibits both butyrylcholinesterase and acetylcholinesterase;

an H2 antagonist;

a kynurenic hydroxylase inhibitor;

an L-type Ca2+ antagonist or L-type calcium channel blocker;

an mGluR5 antagonist;

a monoamine reuptake inhibitor;

a mu opioid receptor agonist

a nicotinic acetylcholine receptor (nAChR) modulator;

a nicotinic antagonist;

a nitric oxide synthase inhibitor;

a nootropic compound;

an NR1A/2B NMDA antagonist;

an NR2B selective NMDA antagonist;

an omega-3 fatty acid;

an opiate antagonist;

an anticholinergic;

an SSRI (Selective Serotonin Reuptake Inhibitor);

a 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor;

a phosphodiesterase (PDE) inhibitor such as a phosphodiesterase 4 (PDE4) inhibitor or a phosphodiesterase 2 (PDE2) inhibitor; and

carbidopa.

2. The use according to claim 1,

wherein the (mTOR) complex 1 (mTORC1) inhibitor is rapamycin;

wherein the 5-HT1a/2a/alpha-2 antagonist is mirtazapine;

wherein the 5-HT2a inverse agonist is selected from ACP103 (pimvaserin), nelotanserin, eplivanserin, or AC-90179 [2-(4-Methoxyphenyl)-N-(4-methyl-benzyl)-N-(1-methyl-piperidin-4-yl)-acetamide Hydrochloride]);

wherein the adenosine A2a receptor antagonist is selected from istradefylline (KW-2,3-triazol 2-yl)-9 H-purin-6-ylamine));

wherein the alpha-1 adrenoceptor antagonist is selected from HEAT (2-[[beta-(-4-hydroxyphenyl)ethyl]aminomethyl]-1-tetralone), alfuzosin, doxazosin, moxisylyte, prazosin, or trimazosin;

wherein the alpha-2 adrenergic receptor antagonist is selected from idazoxan, fipamezole (JP1730), atipamezole, mianserin, phentolamine, or tolazoline;

wherein the AMPA antagonist is E2007 (perampanel);

wherein the AMPA/kainite antagonist is LY300164 [7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo(4,5H)-2,3-benzodiazepine];

wherein the anticonvulsant is selected from primidone, zonisamide, levetiracetam, mesuximide, eslicarbazepine acetate, or pregabalin;

wherein the beta-2 antagonist is selected from propranolol, alprenolol, carteolol, nadolol, sotalol, or timolol;

wherein the CB agonist is selected from nabilone or WIN55,212-2 ((R)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate);

wherein the D2/5-HT2A+ antagonist is clozapine or quetiapine;

wherein the dopaminergic stabilizer is selected from ACR325, aripiprazole, or pridopidine;

wherein the dopaminergic function enhancer/glutamate release inhibitor is safinamide;

wherein the combination of the MAO-B inhibitor and acetylcholinesterase inhibitor is selected from rasagiline, selegiline, safinamide, or EVT-302 (Evotec AG) in combination with ladostigil (TV-3326);

wherein the acetylcholinesterase inhibitor is doepezil;

wherein the cholinesterase inhibitor that inhibits both butyrylcholinesterase and acetylcholinesterase is rivastigmine;

wherein the H2 antagonist is selected from famotidine, cimetidine, burimamide, ranitidine, or metiamide;

wherein the kynurenic hydroxylase inhibitor is selected from Ro 61-8048 (3,4-Dimethoxy-N-[4-(3-nitrophenyl)-2-thiazolyl]benzene sulfonamide or FCE 28833 [(R,S)-2-amino-4-oxo-4-(3',4'-dichlorophenyl) butanoic acid];

wherein the L-type Ca2+ antagonist or L-type calcium channel blocker is selected from isradipine, amlodipine, azelnidipine, cilnidipine, lacidipine, nimodipine, nilvadipine or topiramate;

wherein the mGluR5 antagonist is AFQ056 (6-methyl-2-(phenylethynyl)pyridine);

wherein the monoamine reuptake inhibitor is selected from NS2330 (tesofensine), bicifadine, or DOV-102,677 [(5R)-5-(3,4-dichlorophenyl)bicyclo[3.1.0]hexane];

wherein the nicotinic acetylcholine receptor (nAChR) modulator is selected from an nAChR selective or non-selective agonist; an nAChR selective or non-selective partial agonist; an nAChR competitive antagonist; an nAChR non-competitive antagonist; nicotine (NP002); acetylcholine; choline; epibatidine; lobeline; varenicline; sazetidine-A; DMXB-A (GTS-21, 3-2,4 dimethoxybenzylidene); or SIB-1508Y (3-Ethynyl-5-[(2S)-1-methyl-2-pyrrolidinyl]pyridine);

wherein the nicotinic antagonist is selected from chlorisondamine, d-tubocurarine, mecamylamine, or bupropion;

wherein the nitric oxide synthase inhibitor is selected from 7-nitroindazole or NG-nitro-L-arginine;

wherein the nootropic compound is levitircetam;

wherein the NR1A/2B NMDA antagonist is Cl-1041 (5-[2-[4-(4-fluorobenzyl)piperidin-1-yl]ethylsulfinyl]-2,3-dihydro-1H-benzimidazol-2-one));

wherein the NR2B selective NMDA antagonist is selected from MK0657, CP-101,606 (traxoprodil), eliprodil, Ro 25-6981 ((±)-(R*,S*)-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidine propanol), EVT-101 (Evotec AG), or EVT-103 (Evotec wherein the omega-3 fatty acid is docosahexaenoic acid;

wherein the opiate antagonist is naltrexone;

wherein the anticholinergic is selected from amantadine, ipratropium bromide, oxitropium bromide, or tiotropium;

wherein the SSRI is selected from fluoxetine, paroxetine, sertraline, escitalopram, citalopram, or fluvoxamine;

wherein the 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor is SYN-118, (Synosia Therapeutics);

wherein the PDE4 inhibitor is selected from ronomilast, roflumilast, mesembrine, rolipram, ibudilast, piclamilast, luteolin, cilomilast, tofimilast (9-cyclopentyl-5,6-dihydro-7-ethyl-3-(thien-2-yl)-9H-pyrazolo(3,4-c)-1,2,4-triazolo(4,3-a)pyridine), tipelukast, ibudilast, apremilast ((S)-N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl] acetamide, Celgene Corporation), CC-1088 (a thalidomide analog inhibitor of PDE4, Celgene Corporation), 8-biarylnaphthyridinones such as MK-0952 (Merck), DC-AT-46 (7-benzylamino-6-chloro-2 piperazino-4-pyrrolidino-pteridine), HT-0712 ((3R,5R)-5-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-(3-methylbenzyl)piperidin-2-one, Helicon Therapeutics, Inc.), MEM-1414 (Roche), MEM-1917 (Roche), MEM-1018 (Roche), MEM-1091 (Roche), or DG071 (decode Genetics); and

wherein the PDE2 inhibitor is BAY 60-7550.

3. The use according to claim 1 or claim 2, wherein said movement or motor disorder or side effect thereof is dyskinesia or hyperkinesia.

4. The use according to any one of claims 1 to 3, wherein said dose of eltoprazine is from 2.5 mg/day to 7.5 mg/day.

5. The use according to claim 4, wherein said dose of eltoprazine is 2.5 mg/day.

6. The use according to claim 4, wherein said dose of eltoprazine is 5.0 mg/day.

7. The use according to claim 4, wherein said dose of eltoprazine is 7.5 mg/day.

8. The use according to claim 4, wherein said dose of eltoprazine is 10 mg/day.

9. The use according to any one of claims 1 to 8, wherein said patient is human.

10. The use according to claim 9, wherein said eltoprazine administration does not reduce efficacy of said levodopa or dopamine-related drug administration.

11. The use according to claim 9, wherein said medicament is for administration of eltoprazine or a pharmaceutically acceptable acid addition salt thereof prior to,

concurrently with, or subsequent to administration of at least one anticonvulsant, which is, optionally, selected from primidone or zonisamide.

12. The use according to claim 9, wherein said medicament is for administration of eltoprazine or a pharmaceutically acceptable acid addition salt thereof prior to, concurrently with, or subsequent to administration of at least one mGluR5 antagonist, which is, optionally, AFQ056.

13. The use according to claim 9, wherein said medicament is for administration of eltoprazine or a pharmaceutically acceptable acid addition salt thereof prior to, concurrently with, or subsequent to administration of at least one L-type calcium channel blocker, which is, optionally, selected from isradipine, nimodapine, or nilvadipine.

14. The use according to claim 9, wherein said medicament is for administration of eltoprazine or a pharmaceutically acceptable acid addition salt thereof prior to, concurrently with, or subsequent to administration of at least one NR2B selective NMDA antagonist, which is, optionally, selected from Ro 25-6981, EVT-101, or EVT-103.

15. The use according to claim 9, wherein said medicament is for administration of eltoprazine or a pharmaceutically acceptable acid addition salt thereof prior to, concurrently with, or subsequent to administration of (i) at least one adenosine A2a receptor antagonist, which is, optionally, selected from istradefylline (KW-6002), SYN-115 (4-Hydroxy-N-[4-methoxy-7-(4-morpholinyl)-2-benzothiazolyl]-4-methyl-1-piperidinecarboxamide, or preladenant (SCH420814); or (ii) at least one alpha-2 adrenergic receptor antagonist, which is, optionally, selected from fipamezole (JP1730) or idazoxan.

16. The use according to claim 9, wherein said medicament is for administration of eltoprazine or a pharmaceutically acceptable acid addition salt thereof prior to, concurrently with, or subsequent to administration of at least one 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor, which is, optionally, SYN-118.

17. The use according to claim 9, wherein said medicament is for administration of eltoprazine or a pharmaceutically acceptable acid addition salt thereof prior to,

concurrently with, or subsequent to administration of at least one nicotinic acetylcholine receptor (nAChR) modulator, which is, optionally, selected from an nAChR selective or non-selective agonist; an nAChR selective or non-selective partial agonist; an nAChR competitive antagonist; an nAChR non-competitive antagonist; nicotine (NP002); acetylcholine; choline; epibatidine; lobeline; varenicline; or sazetidine-A.

18. The use according to claim 9, wherein said medicament is for administration of eltoprazine or a pharmaceutically acceptable acid addition salt thereof prior to, concurrently with, or subsequent to administration of at least one phosphodiesterase (PDE) inhibitor, which is, optionally, a phosphodiesterase 2 (PDE2) inhibitor or a phosphodiesterase 4 (PDE4) inhibitor.

19. The use according to any one of claims 1 to 18, wherein said medicament comprising eltoprazine or a pharmaceutically acceptable acid addition salt thereof is to be administered to said patient prior to, concurrently with, or subsequent to the administration of said at least one additional active ingredient; and wherein the administration of said medicament is before or after said patient develops a movement or motor disorder, or side effect thereof, associated with levodopa administration.

20. Use of eltoprazine or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for treating, attenuating, or preventing a movement or motor disorder, or side effect thereof associated with administration of levodopa (L-DOPA), a dopamine-related drug, or a non-L-DOPA-related drug to a patient having Parkinson's disease, wherein said medicament is for use in combination with deep brain stimulation and/or transcranial magnetic stimulation and wherein said eltoprazine or a pharmaceutically acceptable acid addition salt thereof is to be administered to the patient in a dose of from 2.5 mg/day to 10 mg/day.

21. The use according to claim 20, wherein the order of treatment comprises an administration regimen selected from:

(i) said deep brain stimulation and/or transcranial magnetic stimulation precedes treatment of the patient with levodopa (L-DOPA), an L-DOPA-related drug, or a non-L-DOPA-related drug;

(ii) said deep brain stimulation and/or transcranial magnetic stimulation follows treatment of the patient with levodopa (L-DOPA), an L-DOPA-related drug, or a non-L-DOPA-related drug;

(iii) said deep brain stimulation and/or transcranial magnetic stimulation precedes treatment of the patient with eltoprazine or a pharmaceutically acceptable acid addition salt thereof; or

(iv) said deep brain stimulation and/or transcranial magnetic stimulation follows treatment of the patient with eltoprazine or a pharmaceutically acceptable acid addition salt thereof.

22. The use according to claim 20 or claim 21, wherein said medicament comprises eltoprazine or a pharmaceutically acceptable acid addition salt thereof at a dose of from 5 mg/day to 7.5 mg/day.

23. The use according to any one of claims 1 to 22, wherein said dopamine-related drug is selected from a dopamine receptor agonist, which is, optionally, bromocriptine, pergolide, cabergoline, apomorphine, or lisuride; or a non-ergoline dopamine agonist, which is, optionally, ropinirole or pramipexole.