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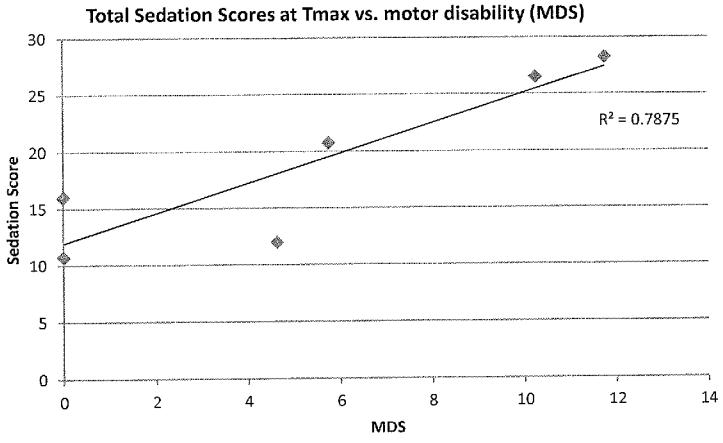
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(54) **Title**: COMPOSITIONS AND METHODS OF REDUCING SEDATION



(57) **Abstract**: Provided are methods and compositions useful in reducing drug-induced sedation in subjects, wherein the compositions comprise an opioid and a dopaminergic agent. The dopaminergic agent is selected from L-DOPA, a dopamine agonist, a MAO inhibitor and a COMT inhibitor or a derivative, prodrug, ester, or pharmaceutically acceptable salt thereof. The opioid and dopaminergic agent are administered simultaneously or sequentially in the method of reducing drug-induced sedation.

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COMPOSITIONS AND METHODS OF REDUCING SEDATION

RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application No. 62/007,425, filed June 4, 2014, the disclosure of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to compositions and methods useful in reducing sedation associated with opioid receptor modulation.

BACKGROUND

[0003] Opioids are commonly used in pain management. Opium, derived from poppy plants is an opioid, as are natural derivatives of opium (opiates), including morphine, methadone, and heroin. The term "opioids" represents a broad class of drugs that includes not only opium and opiates, but also synthetic drugs with the same pharmacological effect as opium including meperidine, fentanyl, alfentanil, sufentanil, and remifentanil. Opioids are powerful analgesics, but opioids are also powerful sedatives. The amount of opioid administered to a patient and the level of pain relief a patient receives from an opioid is currently limited by the patient's level of sedation induced by the opioid. There is a need for compositions and methods for administering an opioid that reduce or substantially eliminate the sedative effects of the opioid.

SUMMARY OF THE INVENTION

[0004] The present invention relates to a combination of opioid agents or related compounds with a dopaminergic agent as a means of reducing sedation caused by opiate or related compounds in subjects and uses thereof.

[0005] The present invention further relates to methods of mitigating opiate adverse effects such as sedation when opiates are used in the following, but not limited to, conditions: pain management, palliative care, anesthesiology (e.g. postoperatively), skin disorders (e.g. pruritus), addictions (detox or management), etc.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings. The figure is a graph showing total sedation scores as a function of motor disability in non-human primates treated with nalbuphine HCl monotherapy.

DETAILED DESCRIPTION OF INVENTION

[0007] The present invention relates to the administration of a dopaminergic agent (e.g., dopamine agonists, L-DOPA, MAO-B inhibitors, and COMT inhibitors) with opioids (e.g. fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, diacetylmorphine, methadone, nalbuphine, pentazocine, butorphanol, etc. and salts thereof, as described in more detail below) or related compounds.

[0008] The administration can be contemporaneous (e.g., co-administration) or sequential. The dopaminergic agent can be administered in an amount sufficient to suppress an opiates' adverse effects, such as sedation.

[0009] The present invention offers a novel method of treatment with the advantage of reducing or eliminating the incidence of adverse effects such as sedation. In certain embodiments, this therapeutic provides superior quality of care and allows a wider range of patients who otherwise may not be suitable for opioid therapy to benefit from this analgesic.

[0010] Unexpectedly, it is now found that there is a correlation between brain dopamine levels in primates, as inferred by the severity of Parkinsonian signs, and sedation produced by an opiate. More specifically, as shown in the Figure, it is now found that parkinsonian motor disability scores (MDS) correlate with sedation scores when nalbuphine is administered in doses of 0.016 mg/kg – 0.50 mg/kg in primates. In other words, severity of dopamine deficiency is a predictor of the sedation severity for the same dose of nalbuphine given to different animals.

[0011] Surprisingly, it is now found that administration of a dopaminergic agent such as L-DOPA to boost brain dopamine levels attenuates and in some embodiments completely attenuates, any opioid sedation in the same cohort of animals. With respect to nalbuphine, in subjects with low levels of dopamine it is very surprising that co-administration of L-DOPA

with nalbuphine suppresses such a common adverse effect such as sedation. This could not be anticipated, as generally L-DOPA use is not known to increase alertness, and, in some cases, administration of L-DOPA or dopamine agonists could be associated with adverse effects such as sedation and somnolence or even sudden onset of sleep without warning.

[0012] Preferably the opioid provides the same level of analgesia to a patient when administered in combination with a dopaminergic agent as the same amount of opioid provides when administered alone, however the sedative effects of the opioid are reduced or substantially eliminated when the opioid is administered in combination with the dopaminergic agent. In some embodiments administration of a dopaminergic agent and an opioid does not substantially affect one or more of the pharmacokinetic parameters (e.g T_{max}, C_{max}, AUC) of the dopaminergic agent and/or the opioid compared to when each is administered individually. In some embodiments administration of a dopaminergic agent and an opioid agent does not substantially affect the maximum plasma concentration (Cmax) of the opioid as compared to administration of the opioid alone. In an embodiment where an opioid (e.g. nalbuphine) is administered subcutaneously at a dosage of 0.25 mg/kg, the average Cmax is about 49 ng/mL. In an embodiment where an opioid (e.g. nalbuphine) is administered subcutaneously at a dosage of 0.25 mg/kg and a dopaminergic agent (e.g. L-DOPA) is administered subcutaneously at a dosage of 25 mg/kg, the average Cmax of opioid is about 55 ng/mL. In some embodiments, administration of a dopaminergic agent and opioid does not affect the area under the curve of plasma concentration versus time (AUC) of the opioid as compared to administration of the opioid alone. In an embodiment where an opioid (e.g. nalbuphine) is administered subcutaneously at a dosage of 0.25 mg/kg, the average AUC is about 96 ng*hr/mL. In an embodiment where an opioid (e.g. nalbuphine) is administered subcutaneously at a dosage of 0.25 mg/kg and a dopaminergic agent (e.g. L-DOPA) is administered subcutaneously at a dosage of 25 mg/kg, the average AUC of opioid is about 89 ng*hr/mL. In some embodiments, administration of a dopaminergic agent and an opioid agent does not affect the amount of time the opioid is present at the maximum concentration in blood serum (Tmax) as compared to administration of the opioid alone. In an embodiment where an opioid (e.g. nalbuphine) is administered subcutaneously at a dosage of 0.25 mg/kg, the average Tmax is about 37 min. In an embodiment where an opioid (e.g. nalbuphine) is administered subcutaneously at a dosage of 0.25 mg/kg and a dopaminergic

agent (e.g. L-DOPA) is administered subcutaneously at a dosage of 25 mg/kg, the average Tmax of opioid is about 32 min.

[0013] The present invention encompasses pharmaceutical compositions and methods to reduce or prevent sedation or one or more symptoms of sedation by co-administering a dopaminergic agent when an opioid agent is used in pain management, anesthesia (e.g. postoperatively), skin disorders (e.g. pruritus), addictions (detox or management) and other conditions in a subject. Opiate adverse effects include decreased attentiveness, diminished reactivity, drowsiness, and combinations thereof.

[0014] Compositions for Use With the Present Invention

[0015] In one embodiment, the present invention is a method of reducing, preventing, or substantially eliminating opiate adverse effects such as sedation by administering separately or simultaneously as a composition comprising a (1.) dopaminergic agent and (2.) an opioid agent. In another embodiment, the dosage form includes a dopaminergic agent in an amount or weight ratio relative to an opioid agent sufficient to provide the benefit of the opioid, but the dopaminergic agent is present in sufficient amount to diminish one or more symptoms of decreased attentiveness, diminished reactivity, drowsiness in a patient compared to the same amount of opioid agent alone. In one embodiment the method includes administering a dopaminergic agent and an opioid agent to a patient. In one embodiment the patient is an animal. In one embodiment the animal is a human. In one embodiment the patient is an animal (e.g. a human) in need of treatment with an opioid.

[0016] 1. Dopaminergic Agents

[0017] Exemplary dopaminergic agents for use in certain embodiments of the present invention include one or more of: (a) a dopamine agonist, (b) L-DOPA, (c) an MAO inhibitor, (d) a COMT inhibitor, or (e) a dopamine re-uptake inhibitor. In certain embodiments, the dopaminergic agent is administered in an amount sufficient to reduce or prevent sedation caused by opioid administration.

[0018] (a) Dopamine Agonists

[0019] Dopamine agonists useful in the present invention include, but are not limited to, pramipexole, ropinirole, rotigotine, apomorphine, piribedil, cabergoline, lisuride, and derivatives, prodrugs, esters, and salts thereof.

[0020] In some embodiments a dopamine agonist is administered in a dosage range of about 0.5 mg to about 4 mg, about 1 mg to about 3 mg, about 0.1 mg to about 1 mg, about 0.5 mg to about 2.5 mg, about 2.5 mg to about 4.5 mg, about 4.5 mg to about 7 mg, about 7 mg to about 10 mg, about 0.5 mg to about 10 mg, or about 2 mg to about 8 mg. In some embodiments a dopamine agonist is administered at a dose of about 0.1 mg, about 0.125 mg, about 0.375, about 0.5 mg, about 0.75, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg.

[0021] (b) L-DOPA

[0022] In some embodiments L-DOPA is administered in a dosage range of about 10 mg to about 200 mg, about 30 mg to about 90 mg, about 40 mg to about 80 mg, about 50 mg to about 70 mg, about 20 mg to about 40 mg, about 30 mg to about 50 mg, about 40 mg to about 60 mg, about 60 mg to about 80 mg, about 70 mg to about 90 mg, about 80 mg to about 100 mg, about 25 mg to about 175 mg, about 50 mg to about 150 mg, about 75 mg to about 125 mg, about 10 mg to about 25 mg, about 100 mg to about 125 mg, about 125 mg to about 150 mg, about 150 mg to about 175 mg, or about 175 mg to about 200 mg. In some embodiments L-DOPA is administered in a dosage of about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 175 mg, about 180 mg, about 190 mg, or about 200 mg.

[0023] (c) MAO Inhibitors

[0024] Monoamine oxidase inhibitors (MAO inhibitors) useful in the present invention include, but are not limited to, isocarboxazid, nialamide, phenelzine, hydracarbazine, tranylcypromie, moclobemide, pirlindole, toloxatone, rasagailine, selegiline, linezolid, and derivatives, prodrugs, esters, and salts thereof. In some embodiments the MAO inhibitor is an MAO B inhibitor, while in other embodiments the MAO inhibitor is an MAO A inhibitor.

[0025] In some embodiments an MAO inhibitor is administered in a dosage range of about 0.1 mg to about 200 mg, about 0.1 mg to about 100 mg, about 0.1 mg to about 25 mg, about 0.1 mg to about 10 mg, about 0.1 mg to about 5 mg, about 0.5 mg to about 5 mg, about 0.5 mg to about 2.5 mg, about 1 mg to about 2.5 mg, about 1 mg to about 5 mg, about 1 mg

to about 7.5 mg, about 1 mg to about 10 mg, about 10 mg to about 200 mg, about 25 mg to about 175 mg, about 50 mg to about 150 mg, about 75 mg to about 125 mg, about 10 mg to about 25 mg, about 25 mg to about 50 mg, about 50 mg to about 75 mg, about 75 mg to about 100 mg, about 100 mg to about 125 mg, about 125 mg to about 150 mg, about 150 mg to about 175 mg, or about 175 mg to about 200 mg. In some embodiments an MAO inhibitor is administered at a dose of about 0.1 mg, about 0.25 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg.

[0026] (d) COMT Inhibitors

[0027] Catechol-O-methyl transferase inhibitors (COMT inhibitors) useful in the present invention include, but are not limited to, entacapone, tolcapone, nitecapone, opicapone, and derivatives, prodrugs, esters, and salts thereof.

[0028] In some embodiments a COMT inhibitor is administered in a dosage range of about 10 mg to about 200 mg, about 25 mg to about 175 mg, about 50 mg to about 150 mg, about 75 mg to about 125 mg, about 10 mg to about 25 mg, about 25 mg to about 50 mg, about 50 mg to about 75 mg, about 75 mg to about 100 mg, about 100 mg to about 125 mg, about 125 mg to about 150 mg, about 150 mg to about 175 mg, or about 175 mg to about 200 mg. In some embodiments a COMT inhibitor is administered at a dose of about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg.

[0029] (e) Dopamine Re-Uptake Inhibitors

[0030] Dopamine re-uptake inhibitors useful in the present invention include, but are not limited to, amineptine, bromantane, dexmethylphenidate, difemetorex, fencamfamine,lefetamine, levophacetoperane, medifoxamine, mesocarb, methylphenidate, nomifensine, pipradrol, prolintane, pyrovalerone, adrafinil, armodafinil, bupropion, mazindol, modafinil, nefazodone, sertraline, sibutramine, and derivatives, prodrugs, esters, and salts thereof.

[0031] In some embodiments a dopamine re-uptake inhibitor is administered in a dosage range of about 10 mg to about 200 mg, about 25 mg to about 175 mg, about 50 mg to about

150 mg, about 75 mg to about 125 mg, about 10 mg to about 25 mg, about 25 mg to about 50 mg, about 50 mg to about 75 mg, about 75 mg to about 100 mg, about 100 mg to about 125 mg, about 125 mg to about 150 mg, about 150 mg to about 175 mg, or about 175 mg to about 200 mg. In some embodiments a dopamine re-uptake inhibitor is administered at a dose of about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg.

[0032] 2. Opioid Agents

[0033] Opioid agents (opioid receptor modulators) useful in the present invention include, but are not limited to, one or more of a mu, delta and kappa receptor ligand.

[0034] In certain embodiments, the opioid agent or agents is one or more of: fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, diacetylmorphine, methadone, nalbuphine, pentazocine, butorphanol, alfentanil, buprenorphine, carfentanil, codeine, dezocine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, β-hydroxy-3-methylfentanyl, levomethadryl, levorphanol, lofentanil, meperidine, nalmefene, oxymorphone, pethidine, propoxyphene, sufentanil, tilidine, and tramodol or derivative, prodrug, or pharmaceutically acceptable salt thereof.

[0035] In some embodiments, the opioid agent is nalbuphine HCl.

[0036] In some embodiments the opioid agent is administered in a dosage range of about 0.01 mg to about 100 mg, about 0.01 mg to about 50 mg, about 0.01 mg to about 25 mg, about 0.01 mg to about 10 mg, about 0.01 mg to about 1 mg, about 0.025 mg to about 0.5 mg, about 0.025 mg to about 0.25 mg, about 0.05 mg to about 0.1 mg, about 1 mg to about 250 mg, about 10 mg to about 100 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 40 mg to about 60 mg, about 5 mg to about 25 mg, about 25 mg to about 50 mg, about 50 mg to about 75 mg, about 75 mg to about 100 mg, about 100 mg to about 125 mg, or about 125 mg to about 150 mg. In some embodiments the opioid agent is administered at a dose of about 0.01 mg, about 0.025 mg, about 0.05 mg, about 0.075 mg, about 0.1 mg, about 0.15 mg, about 0.2 mg, about 0.25 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.75 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 2.5 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg,

about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg.

[0037] In some embodiments, one or more opioid agents are administered in an amount sufficient to cause sedation or other adverse effect including such effects described herein.

[0038] Non-limiting examples of compositions comprising a dopamine agonist and an opioid agent in accordance with the invention are provided in Table 1.

[0039] Table 1

Example No.	Dopamine Agonist	Dosage	Opioid Agent	Dosage
1	pramipexole	about 0.125 mg	nalbuphine	about 5 mg to about 25 mg
2	pramipexole	about 0.125 mg	nalbuphine	about 5 mg to about 150 mg
3	pramipexole	about 1.5 mg	nalbuphine	about 5 mg to about 25 mg
4	pramipexole	about 1.5 mg	nalbuphine	about 5 mg to about 150 mg
5	pramipexole	about 0.1 mg to about 4.5 mg	nalbuphine	about 5 mg to about 150 mg
6	pramipexole	about 0.1 mg to about 4.5 mg	pentazocine	about 5 mg to about 150 mg
7	pramipexole	about 0.1 mg to about 4.5 mg	butorphanol	about 5 mg to about 150 mg
8	pramipexole	about 0.1 mg to about 4.5 mg	fentanyl	about 0.01 mg to about 25 mg
9	pramipexole	about 0.1 mg to about 4.5 mg	hydrocodone	about 0.01 mg to about 25 mg
10	pramipexole	about 0.1 mg to about 4.5 mg	hydromorphone	about 0.01 mg to about 25 mg

11	pramipexole	about 0.1 mg to about 4.5 mg	morphine	about 0.01 mg to about 50 mg
12	pramipexole	about 0.1 mg to about 4.5 mg	oxycodone	about 0.01 mg to about 50 mg
13	pramipexole	about 0.1 mg to about 4.5 mg	meperidine	about 1 mg to about 250 mg
14	pramipexole	about 0.1 mg to about 4.5 mg	codeine	about 1 mg to about 250 mg
15	ropinirole	about 0.1 mg to about 25 mg	nalbuphine	about 5 mg to about 150 mg
16	ropinirole	about 0.1 mg to about 25 mg	pentazocine	about 5 mg to about 150 mg
17	ropinirole	about 0.1 mg to about 25 mg	butorphanol	about 5 mg to about 150 mg
18	ropinirole	about 0.1 mg to about 25 mg	fentanyl	about 0.01 mg to about 25 mg
19	ropinirole	about 0.1 mg to about 25 mg	hydrocodone	about 0.01 mg to about 25 mg
20	ropinirole	about 0.1 mg to about 25 mg	hydromorphone	about 0.01 mg to about 25 mg
21	ropinirole	about 0.1 mg to about 25 mg	morphine	about 0.01 mg to about 50 mg
22	ropinirole	about 0.1 mg to about 25 mg	oxycodone	about 0.01 mg to about 50 mg
23	ropinirole	about 0.1 mg to about 25 mg	meperidine	about 1 mg to about 250 mg
24	ropinirole	about 0.1 mg to about 25 mg	codeine	about 1 mg to about 250 mg
25	rotigotine	about 1 mg to about 10 mg	nalbuphine	about 5 mg to about 150 mg

26	rotigotine	about 1 mg to about 10 mg	pentazocine	about 5 mg to about 150 mg
27	rotigotine	about 1 mg to about 10 mg	butorphanol	about 5 mg to about 150 mg
28	rotigotine	about 1 mg to about 10 mg	fentanyl	about 0.01 mg to about 25 mg
29	rotigotine	about 1 mg to about 10 mg	hydrocodone	about 0.01 mg to about 25 mg
30	rotigotine	about 1 mg to about 10 mg	hydromorphone	about 0.01 mg to about 25 mg
31	rotigotine	about 1 mg to about 10 mg	morphine	about 0.01 mg to about 50 mg
32	rotigotine	about 1 mg to about 10 mg	oxycodone	about 0.01 mg to about 50 mg
33	rotigotine	about 1 mg to about 10 mg	meperidine	about 1 mg to about 250 mg
34	rotigotine	about 1 mg to about 10 mg	codeine	about 1 mg to about 250 mg
35	apomorphine	about 1 mg to about 10 mg	nalbuphine	about 5 mg to about 150 mg
36	apomorphine	about 1 mg to about 10 mg	pentazocine	about 5 mg to about 150 mg
37	apomorphine	about 1 mg to about 10 mg	butorphanol	about 5 mg to about 150 mg
38	apomorphine	about 1 mg to about 10 mg	fentanyl	about 0.01 mg to about 25 mg
39	apomorphine	about 1 mg to about 10 mg	hydrocodone	about 0.01 mg to about 25 mg
40	apomorphine	about 1 mg to about 10 mg	hydromorphone	about 0.01 mg to about 25 mg

41	apomorphine	about 1 mg to about 10 mg	morphine	about 0.01 mg to about 50 mg
42	apomorphine	about 1 mg to about 10 mg	oxycodone	about 0.01 mg to about 50 mg
43	apomorphine	about 1 mg to about 10 mg	meperidine	about 1 mg to about 250 mg
44	apomorphine	about 1 mg to about 10 mg	codeine	about 1 mg to about 250 mg
45	piribedil	about 25 mg to about 75 mg	nalbuphine	about 5 mg to about 150 mg
46	piribedil	about 25 mg to about 75 mg	pentazocine	about 5 mg to about 150 mg
47	piribedil	about 25 mg to about 75 mg	butorphanol	about 5 mg to about 150 mg
48	piribedil	about 25 mg to about 75 mg	fentanyl	about 0.01 mg to about 25 mg
49	piribedil	about 25 mg to about 75 mg	hydrocodone	about 0.01 mg to about 25 mg
50	piribedil	about 25 mg to about 75 mg	hydromorphone	about 0.01 mg to about 25 mg
51	piribedil	about 25 mg to about 75 mg	morphine	about 0.01 mg to about 50 mg
52	piribedil	about 25 mg to about 75 mg	oxycodone	about 0.01 mg to about 50 mg
53	piribedil	about 25 mg to about 75 mg	meperidine	about 1 mg to about 250 mg
54	piribedil	about 25 mg to about 75 mg	codeine	about 1 mg to about 250 mg
55	cabergoline	about 0.1 mg to about 4.5 mg	nalbuphine	about 5 mg to about 150 mg

56	cabergoline	about 0.1 mg to about 4.5 mg	pentazocine	about 5 mg to about 150 mg
57	cabergoline	about 0.1 mg to about 4.5 mg	butorphanol	about 5 mg to about 150 mg
58	cabergoline	about 0.1 mg to about 4.5 mg	fentanyl	about 0.01 mg to about 25 mg
59	cabergoline	about 0.1 mg to about 4.5 mg	hydrocodone	about 0.01 mg to about 25 mg
60	cabergoline	about 0.1 mg to about 4.5 mg	hydromorphone	about 0.01 mg to about 25 mg
61	cabergoline	about 0.1 mg to about 4.5 mg	morphine	about 0.01 mg to about 50 mg
62	cabergoline	about 0.1 mg to about 4.5 mg	oxycodone	about 0.01 mg to about 50 mg
63	cabergoline	about 0.1 mg to about 4.5 mg	meperidine	about 1 mg to about 250 mg
64	cabergoline	about 0.1 mg to about 4.5 mg	codeine	about 1 mg to about 250 mg
65	lisuride	about 0.1 mg to about 4.5 mg	nalbuphine	about 5 mg to about 150 mg
66	lisuride	about 0.1 mg to about 4.5 mg	pentazocine	about 5 mg to about 150 mg
67	lisuride	about 0.1 mg to about 4.5 mg	butorphanol	about 5 mg to about 150 mg
68	lisuride	about 0.1 mg to about 4.5 mg	fentanyl	about 0.01 mg to about 25 mg
69	lisuride	about 0.1 mg to about 4.5 mg	hydrocodone	about 0.01 mg to about 25 mg
70	lisuride	about 0.1 mg to about 4.5 mg	hydromorphone	about 0.01 mg to about 25 mg

71	lisuride	about 0.1 mg to about 4.5 mg	morphine	about 0.01 mg to about 50 mg
72	lisuride	about 0.1 mg to about 4.5 mg	oxycodone	about 0.01 mg to about 50 mg
73	lisuride	about 0.1 mg to about 4.5 mg	meperidine	about 1 mg to about 250 mg
74	lisuride	about 0.1 mg to about 4.5 mg	codeine	about 1 mg to about 250 mg

[0040] Non-limiting examples of compositions comprising a COMT inhibitor and an opioid agent in accordance with the invention are provided in Table 2.

[0041] Table 2

Example No.	COMT Inhibitor	Dosage	Opioid Agent	Dosage
75	entacapone	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
76	entacapone	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 25 mg
77	entacapone	about 100 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
78	entacapone	about 100 mg to about 200 mg	nalbuphine	about 5 mg to about 25 mg
79	entacapone	about 200 mg	nalbuphine	about 5 mg to about 25 mg
80	entacapone	about 200 mg	nalbuphine	about 5 mg to about 150 mg
81	entacapone	about 10 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
82	entacapone	about 10 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
83	entacapone	about 10 mg to about	fentanyl	about 0.01 mg to about

		200 mg		25 mg
84	entacapone	about 10 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
85	entacapone	about 10 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
86	entacapone	about 10 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
87	entacapone	about 10 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
88	entacapone	about 10 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
89	entacapone	about 10 mg to about 200 mg	codeine	about 1 mg to about 250 mg
90	tolcapone	about 10 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
91	tolcapone	about 10 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
92	tolcapone	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
93	tolcapone	about 10 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
94	tolcapone	about 10 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
95	tolcapone	about 10 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
96	tolcapone	about 10 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
97	tolcapone	about 10 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
98	tolcapone	about 10 mg to about	meperidine	about 1 mg to about

		200 mg		250 mg
99	tolcapone	about 10 mg to about 200 mg	codeine	about 1 mg to about 250 mg
100	nitecapone	about 10 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
101	nitecapone	about 10 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
102	nitecapone	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
103	nitecapone	about 10 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
104	nitecapone	about 10 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
105	nitecapone	about 10 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
106	nitecapone	about 10 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
107	nitecapone	about 10 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
108	nitecapone	about 10 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
109	nitecapone	about 10 mg to about 200 mg	codeine	about 1 mg to about 250 mg
110	opicapone	about 10 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
111	opicapone	about 10 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
112	opicapone	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
113	opicapone	about 10 mg to about	fentanyl	about 0.01 mg to about

		200 mg		25 mg
114	opicapone	about 10 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
115	opicapone	about 10 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
116	opicapone	about 10 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
117	opicapone	about 10 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
118	opicapone	about 10 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
119	opicapone	about 10 mg to about 200 mg	codeine	about 1 mg to about 250 mg

[0042] Non-limiting examples of of compositions comprising L-DOPA and an opioid agent in accordance with the invention are provided in Table 3.

[0043] Table 3

Example No.	L-DOPA	Dosage	Opioid Agent	Dosage
120	L-DOPA	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
121	L-DOPA	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 25 mg
122	L-DOPA	about 25 mg to about 75 mg	nalbuphine	about 5 mg to about 150 mg
123	L-DOPA	about 25 mg to about 75 mg	nalbuphine	about 5 mg to about 25 mg
124	L-DOPA	about 50 mg	nalbuphine	about 5 mg to about 25 mg
125	L-DOPA	about 50 mg	nalbuphine	about 5 mg to about 150 mg

126	L-DOPA	about 10 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
127	L-DOPA	about 10 mg to about 200 mg	pentazocine	about 5 mg to about 25 mg
128	L-DOPA	about 25 mg to about 75 mg	pentazocine	about 5 mg to about 150 mg
129	L-DOPA	about 25 mg to about 75 mg	pentazocine	about 5 mg to about 25 mg
130	L-DOPA	about 50 mg	pentazocine	about 5 mg to about 25 mg
131	L-DOPA	about 50 mg	pentazocine	about 5 mg to about 150 mg
132	L-DOPA	about 10 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
133	L-DOPA	about 10 mg to about 200 mg	butorphanol	about 5 mg to about 25 mg
134	L-DOPA	about 25 mg to about 75 mg	butorphanol	about 5 mg to about 150 mg
135	L-DOPA	about 25 mg to about 75 mg	butorphanol	about 5 mg to about 25 mg
136	L-DOPA	about 50 mg	butorphanol	about 5 mg to about 25 mg
137	L-DOPA	about 50 mg	butorphanol	about 5 mg to about 150 mg
138	L-DOPA	about 10 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
139	L-DOPA	about 10 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
140	L-DOPA	about 10 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg

141	L-DOPA	about 10 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
142	L-DOPA	about 10 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
143	L-DOPA	about 10 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
144	L-DOPA	about 10 mg to about 200 mg	codeine	about 1 mg to about 250 mg

[0044] Non-limiting examples of compositions comprising a MAO inhibitor and an opioid agent in accordance with the invention are provided in Table 4.

[0045] Table 4

Example No.	MAO Inhibitor	Dosage	Opioid Agent	Dosage
145	selegiline	about 1 mg to about 25 mg	nalbuphine	about 5 mg to about 150 mg
146	selegiline	about 1 mg to about 25 mg	nalbuphine	about 5 mg to about 25 mg
147	selegiline	about 5 mg to about 25 mg	nalbuphine	about 5 mg to about 150 mg
148	selegiline	about 5 mg to about 25 mg	nalbuphine	about 5 mg to about 25 mg
149	selegiline	about 1 mg	nalbuphine	about 5 mg to about 150 mg
150	selegiline	about 5 mg	nalbuphine	about 5 mg to about 150 mg
151	selegiline	about 1 mg to about 25 mg	pentazocine	about 5 mg to about 150 mg
152	selegiline	about 1 mg to about 25 mg	butorphanol	about 5 mg to about 150 mg
153	selegiline	about 1 mg to about	fentanyl	about 0.01 mg to about

		25 mg		25 mg
154	selegiline	about 1 mg to about 25 mg	hydrocodone	about 0.01 mg to about 25 mg
155	selegiline	about 1 mg to about 25 mg	hydromorphone	about 0.01 mg to about 25 mg
156	selegiline	about 1 mg to about 25 mg	morphine	about 0.01 mg to about 50 mg
157	selegiline	about 1 mg to about 25 mg	oxycodone	about 0.01 mg to about 50 mg
158	selegiline	about 1 mg to about 25 mg	meperidine	about 1 mg to about 250 mg
159	selegiline	about 1 mg to about 25 mg	codeine	about 1 mg to about 250 mg
160	isocarbaxazid	about 10 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
161	isocarbaxazid	about 10 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
162	isocarbaxazid	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
163	isocarbaxazid	about 10 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
164	isocarbaxazid	about 10 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
165	isocarbaxazid	about 10 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
166	isocarbaxazid	about 10 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
167	isocarbaxazid	about 10 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
168	isocarbaxazid	about 10 mg to about	meperidine	about 1 mg to about

		200 mg		250 mg
169	isocarbaxazid	about 10 mg to about 200 mg	codeine	about 1 mg to about 250 mg
170	phenelzine sulfate	about 10 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
171	phenelzine sulfate	about 10 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
172	phenelzine sulfate	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
173	phenelzine sulfate	about 10 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
174	phenelzine sulfate	about 10 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
175	phenelzine sulfate	about 10 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
176	phenelzine sulfate	about 10 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
177	phenelzine sulfate	about 10 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
178	phenelzine sulfate	about 10 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
179	phenelzine sulfate	about 10 mg to about 200 mg	codeine	about 1 mg to about 250 mg
180	tranylcypromine sulfate	about 10 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
181	tranylcypromine sulfate	about 10 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
182	tranylcypromine sulfate	about 10 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
183	tranylcypromine	about 10 mg to about	fentanyl	about 0.01 mg to about

	sulfate	200 mg		25 mg
184	tranylcypromine sulfate	about 10 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
185	tranylcypromine sulfate	about 10 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
186	tranylcypromine sulfate	about 10 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
187	tranylcypromine sulfate	about 10 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
188	tranylcypromine sulfate	about 10 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
189	tranylcypromine sulfate	about 10 mg to about 200 mg	codeine	about 1 mg to about 250 mg
170	rasagaline	about 0.1 mg to about 1 mg	pentazocine	about 5 mg to about 150 mg
171	rasagaline	about 0.1 mg to about 1 mg	butorphanol	about 5 mg to about 150 mg
172	rasagaline	about 0.1 mg to about 1 mg	nalbuphine	about 5 mg to about 150 mg
173	rasagaline	about 0.1 mg to about 1 mg	nalbuphine	about 5 mg to about 150 mg
174	rasagaline	about 0.5 mg	nalbuphine	about 5 mg to about 150 mg
175	rasagaline	about 1 mg	nalbuphine	about 5 mg to about 150 mg
176	rasagaline	about 0.1 mg to about 1 mg	fentanyl	about 0.01 mg to about 25 mg
177	rasagaline	about 0.1 mg to about 1 mg	hydrocodone	about 0.01 mg to about 25 mg
178	rasagaline	about 0.1 mg to	hydromorphone	about 0.01 mg to about

		about 1 mg		25 mg
179	rasagaline	about 0.1 mg to about 1 mg	morphine	about 0.01 mg to about 50 mg
180	rasagaline	about 0.1 mg to about 1 mg	oxycodone	about 0.01 mg to about 50 mg
181	rasagaline	about 0.1 mg to about 1 mg	meperidine	about 1 mg to about 250 mg
182	rasagaline	about 0.1 mg to about 1 mg	codeine	about 1 mg to about 250 mg

[0046] Non-limiting examples of compositions comprising a dopamine re-uptake inhibitor and an opioid agent in accordance with the invention are provided in Table 5.

[0047] Table 5

Example No.	Dopamine reuptake Inhibitor	Dosage	Opioid Agent	Dosage
183	amineptine	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
184	amineptine	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
185	amineptine	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
186	amineptine	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
187	amineptine	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
188	amineptine	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
189	amineptine	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
190	amineptine	about 1 mg to about	oxycodone	about 0.01 mg to

		200 mg		about 50 mg
191	amineptine	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
192	amineptine	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
193	bromantane	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
194	bromantane	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
195	bromantane	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
196	bromantane	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
197	bromantane	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
198	bromantane	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
199	bromantane	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
200	bromantane	about 1 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
201	bromantane	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
202	bromantane	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
203	dexmethylphenidate	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
204	dexmethylphenidate	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
205	dexmethylphenidate	about 1 mg to about	butorphanol	about 5 mg to about

		200 mg		150 mg
206	dexmethylphenidate	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
207	dexmethylphenidate	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
208	dexmethylphenidate	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
209	dexmethylphenidate	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
210	dexmethylphenidate	about 1 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
211	dexmethylphenidate	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
212	dexmethylphenidate	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
213	difemetorex	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
214	difemetorex	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
215	difemetorex	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
216	difemetorex	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
217	difemetorex	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
218	difemetorex	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
219	difemetorex	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
220	difemetorex	about 1 mg to about	oxycodone	about 0.01 mg to

		200 mg		about 50 mg
221	difemetorex	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
222	difemetorex	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
223	fencamfamine	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
224	fencamfamine	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
225	fencamfamine	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
226	fencamfamine	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
227	fencamfamine	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
228	fencamfamine	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
229	fencamfamine	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
230	fencamfamine	about 1 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
231	fencamfamine	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
232	fencamfamine	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
233	lefetamine	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
234	lefetamine	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
235	lefetamine	about 1 mg to about	butorphanol	about 5 mg to about

		200 mg		150 mg
236	lefetamine	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
237	lefetamine	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
238	lefetamine	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
239	lefetamine	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
240	lefetamine	about 1 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
241	lefetamine	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
242	lefetamine	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
243	levophacetoperane	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
244	levophacetoperane	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
245	levophacetoperane	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
246	levophacetoperane	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
247	levophacetoperane	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
248	levophacetoperane	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
249	levophacetoperane	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
250	levophacetoperane	about 1 mg to about	oxycodone	about 0.01 mg to

		200 mg		about 50 mg
251	levophacetoperane	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
252	levophacetoperane	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
253	medifoxamine	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
254	medifoxamine	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
255	medifoxamine	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
256	medifoxamine	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
257	medifoxamine	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
258	medifoxamine	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
259	medifoxamine	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
260	medifoxamine	about 1 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
261	medifoxamine	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
262	medifoxamine	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
263	mesocarb	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
264	mesocarb	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
265	mesocarb	about 1 mg to about	butorphanol	about 5 mg to about

		200 mg		150 mg
266	mesocarb	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
267	mesocarb	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
268	mesocarb	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
269	mesocarb	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
270	mesocarb	about 1 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
271	mesocarb	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
272	mesocarb	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
273	methylphenidate	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
274	methylphenidate	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
275	methylphenidate	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
276	methylphenidate	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
277	methylphenidate	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
278	methylphenidate	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
279	methylphenidate	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
280	methylphenidate	about 1 mg to about	oxycodone	about 0.01 mg to

		200 mg		about 50 mg
281	methylphenidate	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
282	methylphenidate	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
283	nomifensine	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
284	nomifensine	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
285	nomifensine	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
286	nomifensine	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
287	nomifensine	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
288	nomifensine	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
289	nomifensine	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
290	nomifensine	about 1 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
291	nomifensine	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
292	nomifensine	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
293	pipradrol	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
294	pipradrol	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
295	pipradrol	about 1 mg to about	butorphanol	about 5 mg to about

		200 mg		150 mg
296	pipradrol	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
297	pipradrol	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
298	pipradrol	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
299	pipradrol	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
300	pipradrol	about 1 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
301	pipradrol	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
302	pipradrol	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
303	prolintane	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
304	prolintane	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
305	prolintane	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
306	prolintane	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
307	prolintane	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
308	prolintane	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
309	prolintane	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
310	prolintane	about 1 mg to about	oxycodone	about 0.01 mg to

		200 mg		about 50 mg
311	prolintane	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
312	prolintane	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg
313	pyrovalerone	about 1 mg to about 200 mg	nalbuphine	about 5 mg to about 150 mg
314	pyrovalerone	about 1 mg to about 200 mg	pentazocine	about 5 mg to about 150 mg
315	pyrovalerone	about 1 mg to about 200 mg	butorphanol	about 5 mg to about 150 mg
316	pyrovalerone	about 1 mg to about 200 mg	fentanyl	about 0.01 mg to about 25 mg
317	pyrovalerone	about 1 mg to about 200 mg	hydrocodone	about 0.01 mg to about 25 mg
318	pyrovalerone	about 1 mg to about 200 mg	hydromorphone	about 0.01 mg to about 25 mg
319	pyrovalerone	about 1 mg to about 200 mg	morphine	about 0.01 mg to about 50 mg
320	pyrovalerone	about 1 mg to about 200 mg	oxycodone	about 0.01 mg to about 50 mg
321	pyrovalerone	about 1 mg to about 200 mg	meperidine	about 1 mg to about 250 mg
322	pyrovalerone	about 1 mg to about 200 mg	codeine	about 1 mg to about 250 mg

[0048] In certain embodiments the weight ratio of dopaminergic agent to opioid agent is in the range of: 50000:1 to 1:50000, 20000:1 to 1:20000, 10000:1 to 1:10000, 5000:1 to 1:5000, 2500:1 to 1:2500, 2000:1 to 1:2000, 1500:1 to 1:1500, 1000:1 to 1:1000, 750:1 to 1:750, 500:1 to 1:500, 250:1 to 1:250, 100:1 to 1:100, 75:1 to 1:75, 50:1 to 1:50, 25:1 to 1:25, 20:1 to 1:20, 2:1 to 1:2: 4:1 to 1:2, 1:1 to 1:50000, 1:1 to 1:20000, 1:1 to 1:10000, 1:1

to 1:7500, 1:1 to 1:5000, 1:1 to 1:2500, 1:1 to 1:1000, 1:1 to 1:750, 1:1 to 1:500, 1:1 to 1:250, 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:20, 1:1 to 1:10, 1:1 to 1:5, 1:1 to 50000:1, 1:1 to 20000:1, 1:1 to 10000:1, 1:1 to 7500:1, 1:1 to 5000:1, 1:1 to 2500:1, 1:1 to 1000:1, 1:1 to 750:1, 1:1 to 500:1, 1:1 to 250:1, 1:1 to 100:1, 1:1 to 75:1, 1:1 to 50:1, 1:1 to 25, 1:1 to 20:1, 1:1 to 10:1, 1:1 to 5:1.

[0049] In an embodiment, a dopaminergic agent and an opioid agent can be formulated separately or together in various administration vehicles, including, but not limited to, tablet, orally disintegrating tablet, capsule, syrup, suppository, transdermal delivery system (e.g. skin patch), inhalable powder, inhalable aerosol, sublingual spray, intranasal spray and intranasal aerosol. In some embodiments a dopaminergic agent and/or an opioid agent may be administered via oral, rectal, buccal, intranasal or transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, sublingually, orally, topically, or as an inhalant. The major advantage of utilizing such a non-injectable form is to improve the quality of life and compliance for patients requiring repeated or chronic administration. In some embodiments a dopaminergic agent and an opioid agent may be administered concomitantly in the same formulation and administration vehicle. In some embodiments the dopaminergic agent may be administered in separate formulations but via the same administration vehicle (e.g. two tablets, one comprising a dopaminergic agent and one comprising an opioid agent). In some embodiments a dopaminergic agent and an opioid agent may be administered by different administration vehicles. For example, in some embodiments one of the dopaminergic agent and the opioid agent may be administered in an injectable form and the other may be administered in a non-injectable form.

[0050] In some embodiments, the present invention includes one or more additional constituents having pharmacological activity. Such additional constituents include mu-opioid receptor antagonists/kappa-opioid receptor agonists, components for suppressing peripheral metabolism (e.g., carbidopa and benserazide), and/or other additional active ingredients such as, for instance, painkillers, antibacterial, antiviral or antifungal agents, vitamins, immune system fortifiers, homeopathic agents, antihypertensive medication, nootropics, any combinations thereof, and so forth.

[0051] Other Constituents

[0052] In some embodiments of the invention, inactive ingredients or other additives may be included. Such inactive ingredients can be used for bulk, drug release properties, as a carrier, for facilitating digestion, and for other purposes, as known in the art. In one example, a formulation includes Nalbuphine, L-DOPA, a release modifying component, and optional additives.

[0053] In some embodiments a composition includes a release-modifying component. Preferably, the one or more materials prolong the release of opioid (e.g. nalbuphine) from the composition. Examples of release-modifying materials include carbomers, carboxymethylcellulose, hydroxypropylmethylcellulose, biodegradeable polymers, as well as any combination thereof. Carbomers, e.g., Carbopole resins are compounds that are carboxyacrylic or carboxyvinyl polymers.

[0054] Additives such as, for example, lactose, microcrystalline cellulose, colloidal silica, lubricants, acid stabilizers, disintegrants and many others also can be included.

[0055] Some additives that can be employed include, but are not limited to ammonio-methacrylate copolymers, NF, fumaric acid, NF, povidone, USP, sodium lauryl sulfate, NF, sugar starch, NF, and talc, USP, gelatin, titanium dioxide, lactose, hydroxypropyl methylcellulose, colloidal silicon dioxide, stearic acid, lactic acid, citric acid, vitamin E, EDTA, butylated hydroxyanisole, propylparaben, methylparaben, sodium benzoate, potassium benzoate, benzalkonium chloride, benzoic acid, sorbic acid, PEG 400, carrageenan products (such as Viscarin 328, Gelcarin 812, and Seaspen), microcrystalline cellulose (MCC), colloid silicon oxide (e.g., Aerosil) and others.

[0056] In some embodiments a composition may include a lubricant. Examples of lubricants include magnesium stearate, calcium stearate, talcum, their mixtures and others, as known in the art. It is preferably to use magnesium stearate in the quantity of 0.2-1.5% and talcum in the quantity of 0.8-3.0%.

[0057] In some embodiments a composition may include lactose. Lactose is a neutral filler, providing optimal rheological properties of the granulated material and tablet mass in the manufacture of the tablet. Lactose having particle size of 70-200 microns, are preferred. Also preferred are spherical or nearly spherical lactose particles.

[0058] In a specific, non-limiting example, a non-injectable formulation is a capsule containing 5-150 mg (e.g. 5, 10, 60, 90, or 150 mg) of nalbuphine, 20-100 mg of L-DOPA, and one or more of the inactive ingredients such as ammonio-methacrylate copolymers, NF, fumaric acid, NF, povidone, USP, sodium lauryl sulfate, NF, sugar starch spheres, NF, and talc, USP, (and their suitable analogues). The capsule shell can contain ink, gelatin, titanium dioxide, (and their suitable analogues).

[0059] In another specific, non-limiting example, a non-injectable formulation is a tablet including 5-150 mg (e.g. 5, 10, 60, 90, or 150 mg) of nalbuphine, 10-200 mg of L-DOPA, and one or more of the inactive ingredients such as, lactose, hydroxypropyl methylcellulose, colloidal silicon dioxide, and/or stearic acid. Known analogues of the inactive components also can be used.

[0060] In another specific, non-limiting example a tablet form includes by weight: pramipexole 0.1-4.5 mg; nalbuphine chloride 5-150 mg. A tablet may also contain hypromellose, corn starch, carbomer homopolymer, colloidal silicon dioxide, magnesium stearate, or a combination thereof.

[0061] Another example of the formulation in tablet form includes by weight: entacapone 10-200 mg; nalbuphine chloride: 5-150 mg. A tablet may also contain starch or hydroxypropyl cellulose, pregelatinized starch, crospovidone, microcrystalline cellulose, magnesium stearate, or a combination thereof.

[0062] Another example of the formulation in tablet form includes by weight: L-DOPA 10-200 mg; carbidopa 5-25 mg; nalbuphine chloride: 5-150mg. A tablet may also contain starch or hydroxypropyl cellulose, pregelatinized starch, crospovidone, microcrystalline cellulose, magnesium stearate, or a combination thereof.

[0063] Yet another example of the formulation in tablet form includes by weight: L-DOPA 25-50 mg; carbidopa 6-12.5 mg; nalbuphine chloride: 5-150 mg. A tablet may also contain starch or hydroxypropyl cellulose, pregelatinized starch, crospovidone, microcrystalline cellulose, magnesium stearate, or a combination thereof.

[0064] Another example of the formulation in tablet form includes by weight: L-DOPA 10-200 mg; carbidopa 5-25 mg; entacapone 10-200 mg; nalbuphine chloride: 5-150 mg. A tablet may also contain starch or hydroxypropyl cellulose, pregelatinized

starch, crospovidone, microcrystalline cellulose, magnesium stearate, or a combination thereof.

[0065] Yet another example of the formulation in tablet form includes by weight: L-DOPA 25-50 mg; carbidopa 6-12.5 mg; entacapone 10-200 mg; nalbuphine chloride: 5-150 mg. A tablet may also contain starch or hydroxypropyl cellulose, pregelatinized starch, crospovidone, microcrystalline cellulose, magnesium stearate, or a combination thereof.

[0066] Without wishing to be held by a specific mechanism of action, it is believed that compounds employed in the present formulation can form a protective matrix around active ingredients and modify its release kinetics from the formulation.

[0067] A tablet or caplet described above can be formulated at a desired dosage, for example, it can contain 5-150 mg of nalbuphine chloride and 0.1-4.5 mg pramipexole or 10-200 mg of COMT inhibitor or 10-200 mg of L-DOPA.

[0068] The non-injectable formulations disclosed herein can be prepared by combining one or more agonist-antagonists with any other active or inactive ingredients. The process is not limited to any particular order of adding ingredients. One or more ingredients can be added simultaneously and sequential additions also can be carried out. Laboratory, pilot plant and commercial operations can be employed. Mixing, spray drying, emulsifying, purifying, compounding, and many other additional steps known in the fields of drug synthesis and manufacture also can be used to produce the non-injectable formulation.

[0069] Methods to Reduce Opioid Sedation

[0070] In an embodiment, the present invention is a method of reducing, preventing, or eliminating opiate adverse effects such as sedation by administering separately, or simultaneously as a composition, comprising a dopaminergic agent and an opioid agent. In an embodiment the dopaminergic agent is one or more of (a) a dopamine agonist, (b) L-DOPA, (c) an MAO inhibitor, (d) a COMT inhibitor, or (e) a dopamine re-uptake inhibitor.

[0071] In an embodiment, the present invention is a method of reducing, preventing, or eliminating opiate adverse effects such as sedation by administering separately or simultaneously as a composition comprising a dopamine agonist and an opioid agent. In an embodiment a dopamine agonist is administered at a dosage range of about 0.1 mg to about 25 mg, and an opioid agent is administered at a dosage range of about 0.01 mg to about 150 mg. In some embodiments the dopamine agonist is selected from the group consisting of

pramipexole, ropinirole, rotigotine, apomorphine, piribedil, cabergoline, lisuride, and derivatives, prodrugs, esters, and salts thereof. In some embodiments the opioid agent is selected from the group consisting of fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, diacetylmorphine, methadone, alfentanil, buprenorphine, carfentanil, codeine, dezocine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, β-hydroxy-3-methylfentanyl, levomethadryl, levorphanol, lofentanil, meperidine, nalmefene, oxymorphone, pethidine, propoxyphene, sufentanil, tilidine, nalbuphine, pentazocine, butorphanol, derivatives, prodrugs, esters, and salts thereof. In one embodiment the dopamine agonist is pramipexole and the opioid agent is nalbuphine.

[0072] In an embodiment, the present invention is a method of reducing, preventing, or eliminating opiate adverse effects such as sedation by administering separately or simultaneously as a composition comprising a COMT inhibitor and an opioid agent. In an embodiment a COMT inhibitor is administered at a dosage range of about 10 mg to about 200 mg, and an opioid agent is administered at a dosage range of about 0.01 mg to about 150 mg. In some embodiments the COMT inhibitor is selected from the group consisting of entacapone, tolcapone, nitecapone, opicapone, and derivatives, prodrugs, esters, and salts thereof. In some embodiments the opioid agent is selected from the group consisting of fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, diacetylmorphine, methadone, alfentanil, buprenorphine, carfentanil, codeine, dezocine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, β-hydroxy-3-methylfentanyl, levomethadryl, levorphanol, lofentanil, meperidine, nalmefene, oxymorphone, pethidine, propoxyphene, sufentanil, tilidine, nalbuphine, pentazocine, butorphanol, derivatives, prodrugs, esters, and salts thereof. In one embodiment the COMT inhibitor is entacapone and the opioid agent is nalbuphine.

[0073] In an embodiment, the present invention is a method of reducing, preventing, or eliminating opiate adverse effects such as sedation by administering separately or simultaneously as a composition comprising L-DOPA and an opioid agent. In an embodiment L-DOPA is administered at a dosage range of about 10 mg to about 200 mg, and an opioid agent is administered at a dosage range of about 5 mg to about 150 mg. In some embodiments the opioid agent is selected from the group consisting of fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, diacetylmorphine, methadone,

alfentanil, buprenorphine, carfentanil, codeine, dezocine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, β-hydroxy-3-methylfentanyl, levomethadryl, levorphanol, lofentanil, meperidine, nalmefene, oxymorphone, pethidine, propoxyphene, sufentanil, tilidine, nalbuphine, pentazocine, butorphanol, derivatives, prodrugs, esters, and salts thereof. In one embodiment the opioid agent is nalbuphine.

[0074] In an embodiment, the present invention is a method of reducing, preventing, or eliminating opiate adverse effects such as sedation by administering separately or simultaneously as a composition comprising a MAO inhibitor and an opioid agent. In an embodiment a MAO inhibitor is administered at a dosage range of about 0.5 mg to about 10 mg, and an opioid agent is administered at a dosage range of about 0.01 mg to about 150 mg. In some embodiments the MAO inhibitor is selected from the group consisting of isocarboxazid, nialamide, phenelzine, hydracarbazine, tranylcypromie, moclobemide, pirlindole, toloxatone, rasagiline, selegiline, linezolid, and derivatives, prodrugs, esters, and salts thereof. In some embodiments the opioid agent is selected from the group consisting of fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, diacetylmorphine, methadone, alfentanil, buprenorphine, carfentanil, codeine, dezocine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, β-hydroxy-3-methylfentanyl, levomethadryl, levorphanol, lofentanil, meperidine, nalmefene, oxymorphone, pethidine, propoxyphene, sufentanil, tilidine, nalbuphine, pentazocine, butorphanol, derivatives, prodrugs, esters, and salts thereof. In one embodiment the MAO inhibitor is an MAO B inhibitor. In one embodiment the MAO inhibitor is selegiline and the opioid agent is nalbuphine. In another embodiment the MAO inhibitor is rasagiline and the opioid agent is nalbuphine.

[0075] In some embodiments the opioid agent is administered in a dosage range of about 0.01 mg to about 100 mg, about 0.01 mg to about 10 mg, about 0.01 mg to about 1 mg, about 0.025 mg to about 0.5 mg, about 0.025 mg to about 0.25 mg, about 0.05 mg to about 0.1 mg, about 10 mg to about 100 mg, about 20 mg to about 80 mg, about 25 mg to about 75 mg, about 40 mg to about 60 mg, about 5 mg to about 25 mg, about 25 mg to about 50 mg, about 50 mg to about 75 mg, about 75 mg to about 100 mg, about 100 mg to about 125 mg, or about 125 mg to about 150 mg. In some embodiments the opioid agent is administered at a dose of about 0.01 mg, about 0.025 mg, about 0.05 mg, about 0.075 mg, about 0.1 mg, about

0.15 mg, about 0.2 mg, about 0.25 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.75 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 2.5 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg.

[0076] In one embodiment the dopaminergic agent is administered to a subject at a dose of about 0.1 mg to about 200 mg and the opioid agent is administered to the subject at a dose of about 0.01 mg to about 150 mg.

[0077] Additionally, certain embodiments of the present invention includes a method of reducing or eliminating opiate adverse effects such as sedation comprising administering to a subject an injectable form of mu-opioid receptor antagonist/kappa-opioid receptor agonist along with L-DOPA or dopamine agonist when warranted by subject's medical condition.

[0078] In one embodiment, the present invention is a method of reducing or eliminating opiate adverse effects such as sedation by administering L-DOPA to a subject as a non-injectable composition comprising: (i) pharmaceutically acceptable oral formulation comprising COMT inhibitor in an amount of at least 10 mg and (ii) free-base nalbuphine, its prodrug or pharmaceutically acceptable salt of nalbuphine in an amount of at least 1 milligram and (iii) an inactive component; and wherein the formulation is in tablet or capsule or oral liquid form.

[0079] In another embodiment, the present invention is a method of reducing or eliminating opiate adverse effects such as sedation by administering L-DOPA to a subject a non-injectable composition comprising: (i) pharmaceutically acceptable oral formulation comprising L-DOPA in an amount of at least 10 mg with or without components suppressing peripheral metabolism such as carbidopa and benserazide and (ii) free-base nalbuphine, its prodrug or pharmaceutically acceptable salt of nalbuphine in an amount of at least 1 milligram and (iii) an inactive component; and wherein the formulation is in tablet or capsule or oral liquid form.

[0080] In a further embodiment, the present invention pertains to selecting a subject with low dopamine levels by administering nalbuphine and measuring sedation as means of early detection, assessment of risk factors or diagnostics of a relevant condition or a disease.

[0081] Example 1. Drug effects on the nervous system (Sedation) in tests of Nalbuphine monotherapy.

[0082] Parkinsonian non-human primates (n=6) were injected (s.c.) with Nalbuphine HCl (NB, dissolved in saline) and evaluated for changes in parkinsonian motor disability (MDS) and drug effects on the nervous system (DENS). Evaluations were performed immediately before injection (baseline), at 30 minutes post-injection and again every 20 minutes thereafter for 110 minutes or until effects were no longer observable. Five NB doses (0.0, 0.016, 0.05, 0.16, 0.50 mg/kg) were tested in each animal with each dose tested 3 times in all animals.

	NB DOSE (mg/kg)				
Sedation Items:	**0.00**	**0.016**	**0.05**	**0.16**	**0.5**
Attentiveness	0.33 ± 0.25	2.00 ± 0.73	2.75 ± 1.07	3.17 ± 1.51	5.17 ± 1.34
Reactivity	0.19 ± 0.12	0.67 ± 0.36	1.58 ± 0.85	4.1 ± 1.60	6.65 ± 2.15
Eye Movement	0.02 ± 0.02	0.17 ± 0.17	0.54 ± 0.25	2.44 ± 0.94	3.29 ± 1.10
Mouth*	0.21 ± 0.16	0.13 ± 0.09	0.17 ± 0.11	0.00	1.17 ± 1.07
Appetite#	0.29 ± 0.29	0.13 ± 0.13	0.56 ± 0.26	1.48 ± 1.03	4.79 ± 0.78
Total	**1.04**	**3.08**	**5.61**	**11.19**	**21.06**

[0083] *Itemized Sedation scores* (see Uthayathas et al., "Assessment of adverse effects of neurotropic drugs in monkeys with the 'drug effects on the nervous system' (DENS) scale," J Neurosci Methods. 2013 Apr 30; 215(1):97-102, for complete description of the DENS scale, incorporated by reference herein in its entirety). The items in this scale are given in the table

with the exception of "Involuntary Movements", "Bowel" and "Bladder", which were omitted because they were not scored with this scale. Scores are total values from adding all intervals. Higher scores reflect increased sedative effects. All items were evaluated based on comparison with the baseline parkinsonian state. *Mouth (i.e. excessive salivation - drooling) was only scored when it was noticeably increased compared to the baseline parkinsonian state. #Appetite was only scored when it was considered markedly reduced based on the animal's interest in taking treats compared to the baseline parkinsonian state. Values represent the means ± SEM of all animals (n = 6).

[0084] Example 2. Drug effects on the nervous system (Sedation) in tests of Nalbuphine co-administration with LDOPA.

[0085] Animals (n=6) were injected (s.c.) with NB immediately prior to receiving L-dopa (LD; levodopa methyl ester plus 25% benserazide, dissolved in saline and given s.c.). The LD dose was determined individually for each animal based on 'on' response and consistency of dyskinesia. Animals were evaluated for changes in parkinsonian motor disability scores (MDS), drug effects on the nervous system (Sedation) and severity of dyskinesias. Evaluations were performed immediately before injections (baseline), at 30 minutes post-injections and again every 20 minutes thereafter until scores returned to 50-100% of baseline. Each of 5 NB doses (0.0, 0.03, 0.06, 0.13, 0.25 mg/kg) was tested in combination with LD (the same dose for all tests) in each animal with each test repeated 3 times.

	NB DOSE (mg/kg) with L-DOPA				
Sedation Items:	**0.00**	**0.003**	**0.0625**	**0.125**	**0.25**
Attentiveness	0.00	0.00	0.00	0.00	0.00
Reactivity	0.00	0.00	0.00	0.00	0.00
Eye Movement	0.00	0.00	0.00	0.00	0.00
Mouth*	0.00	0.00	0.00	0.00	0.00

Appetite[#]	0.00	0.00	0.00	0.00	0.00
Total	0.00	0.00	0.00	0.00	0.00

[0086] *Itemized Sedation scores* (see Uthayathas 2013 for complete description of the DENS scale). The items in this scale are given in the table with the exception of "Involuntary Movements", "Bowel" and "Bladder", which were omitted because they were not scored with DENS scale. Scores are total values from adding all intervals. Higher scores reflect increased sedative effects. All items were evaluated based on comparison with the baseline parkinsonian state. *Mouth (i.e. excessive salivation - drooling) was only scored when it was noticeably increased compared to the baseline parkinsonian state. [#]Appetite was only scored when it was considered markedly reduced based on the animal's interest in taking treats compared to the baseline parkinsonian state. Values represent the mean ± SEM of all animals (n = 6).

[0087] Example 4. Compositions useful to reduce adverse effects such as sedation of Nalbuphine.

[0088] Entacapone 5-40%; Nalbuphine chloride: 5-20%. Tablet contains release modifying component: 10-35%; Colloid silicon oxide e.g., Aerosil: 0.2-3%; Microcrystalline cellulose: 5-20%; Povidone: 1-5%; Lubricants: 0.3-5%; Lactose: the rest. Additionally the tablet could be coated with Opadry YS-1-7027 (white) and ACRYL-EZE (white) with antifoaming emulsion in the following ratio: Opadry YS-1-7027 (white)—16-21.5% ACRYL-EZE (white)—78-83.5%. Antifoaming emulsion—the remaining balance.

[0089] Sustained release: Tablet L-DOPA 5-22%; Nalbuphine chloride: 2.5-22%. Tablet contains release modifying component: 10-35%; Colloid silicon oxide e.g., Aerosil: 0.2-3%; Microcrystalline cellulose: 5-20%; Povidone: 1-5%; Lubricants: 0.3-5%; Lactose: the rest. Additionally the tablet could be coated with Opadry YS-1-7027 (white) and ACRYL-

EZE (white) with antifoaming emulsion in the following ratio: Opadry YS-1-7027 (white)—16-21.5% ACRYL-EZE (white)—78-83.5%. Antifoaming emulsion—the remaining balance.

[0090] Sustained release: Tablet L-DOPA 5-22%; Carbidopa 1.25-5.5%; Nalbuphine chloride: 3-22%. Tablet contains release modifying component: 10-35%; Colloid silicon oxide e.g., Aerosil: 0.2-3%; Microcrystalline cellulose: 5-20%; Povidone: 1-5%; Lubricants: 0.3-5%; Lactose: the rest. Additionally the tablet could be coated with Opadry YS-1-7027 (white) and ACRYL-EZE (white) with antifoaming emulsion in the following ratio: Opadry YS-1-7027 (white)—16-21.5% ACRYL-EZE (white)—78-83.5%. Antifoaming emulsion—the remaining balance.

[0091] The foregoing constructive examples and descriptions of the preferred embodiments should be interpreted as illustrating, rather than as limiting the present invention as defined by the claims. All variations and combinations of the features above are intended to be within the scope of the following claims.

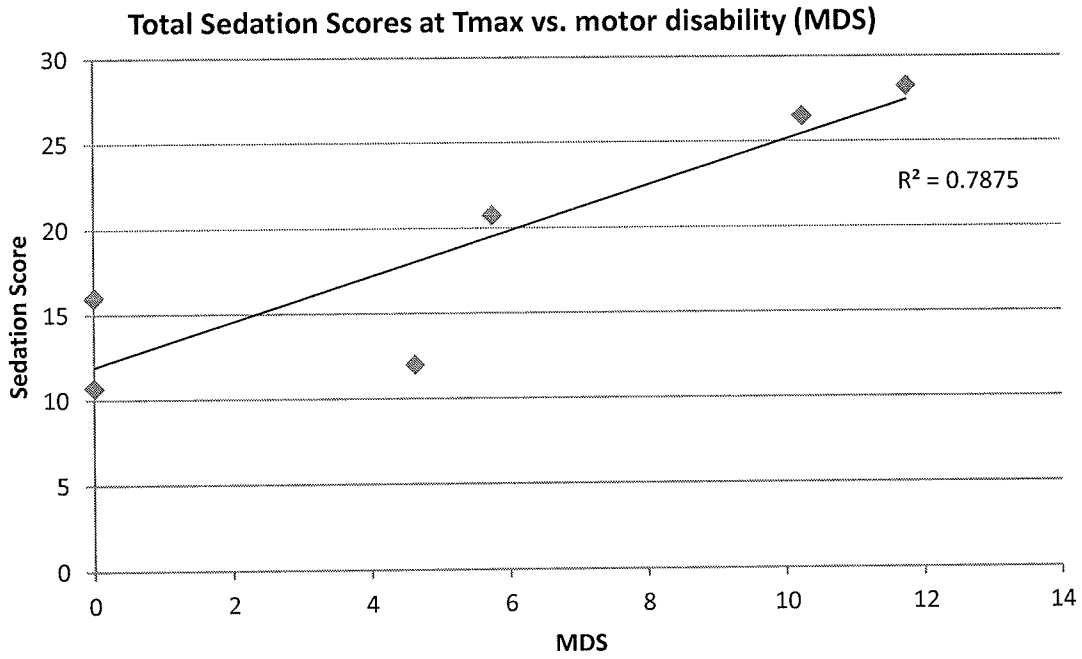
WHAT IS CLAIMED IS:

1. A method of reducing or preventing one or more symptoms of sedation comprising administering a dopaminergic agent and an opioid to a subject.
2. The method of claim 1, wherein the one or more symptoms of sedation are selected from decreased attentiveness, diminished reactivity, drowsiness, and combinations thereof.
3. The method of claim 1, wherein the dopaminergic agent and opioid are administered simultaneously.
4. The method of claim 1, wherein the dopaminergic agent and opioid are administered sequentially.
5. The method of claim 1, wherein the dopaminergic agent is L-DOPA or a derivative, prodrug, ester, or pharmaceutically acceptable salt thereof.
6. The method of claim 1, wherein the dopaminergic agent is a dopamine agonist or a derivative, prodrug, ester, or pharmaceutically acceptable salt thereof.
7. The method of claim 1, wherein the dopaminergic agent is a COMT inhibitor or a derivative, prodrug, ester, or pharmaceutically acceptable salt thereof.
8. The method of claim 1, wherein the dopaminergic agent is a MAO inhibitor or a derivative, prodrug, ester, or pharmaceutically acceptable salt thereof.
9. The method of claim 1, wherein the dopaminergic agent is a dopamine re-uptake inhibitor or a derivative, prodrug, ester, or pharmaceutically acceptable salt thereof.
10. The method of claim 1, wherein the opioid is selected from the group consisting of fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, diacetylmorphine, methadone, alfentanil, buprenorphine, carfentanil, codeine, dezocine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, β-hydroxy-3-methylfentanyl, levomethadryl, levorphanol, lofentanil, meperidine, nalmefene, oxymorphone, pethidine, propoxyphene, sufentanil, tilidine, nalbuphine, pentazocine, butorphanol, derivatives, prodrugs, esters, and salts thereof.
11. The method of claim 10, wherein the dopaminergic agent is selected from L-DOPA, selegiline, rasagiline, tolcapone, entacapone, derivatives, prodrugs, esters, and salts

thereof, and the opioid is selected from nalbuphine, pentazocine, butorphanol, derivatives, prodrugs, esters, and salts thereof.

12. The method of claim 1, wherein the dopaminergic agent is L-DOPA and the opioid is nalbuphine.
13. The method of claim 1, wherein the dopaminergic agent and opioid are administered for treating pain, dermatological disorder, pruritis, addiction or dystonia.
14. A composition comprising a dopaminergic agent and an opioid, wherein the dopaminergic agent and opioid are present in an amount sufficient to provide the benefit of the opioid and diminish one or more symptoms of decreased attentiveness, diminished reactivity, drowsiness in a patient compared to the same amount of opioid agent alone.
15. The composition of claim 14, wherein the dopaminergic agent is L-DOPA, pramipexole, ropinirole, rotigotine, selegiline, rasagiline, tolcapone, entacapone, or a derivative, prodrug, ester, or salt thereof.
16. The composition of claim 14, wherein the opioid is selected from the group consisting of fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, diacetylmorphine, methadone, alfentanil, buprenorphine, carfentanil, codeine, dezocine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, β-hydroxy-3-methylfentanyl, levomethadryl, levorphanol, lofentanil, meperidine, nalmefene, oxymorphone, pethidine, propoxyphene, sufentanil, tilidine, nalbuphine, pentazocine, butorphanol, derivatives, prodrugs, esters, and salts thereof.
17. The composition of claim 16, wherein the opioid is nalbuphine, pentazocine, butorphanol, or a derivative, prodrug, ester, or salt thereof.
18. A composition comprising a dopaminergic agent and an opioid for treating dermatological disorder, pruritis, addiction, dystonia, or a combination thereof, wherein the dopaminergic agent and opioid are present in an amount sufficient to provide the benefit of the opioid and to diminish one or more symptoms of decreased attentiveness, diminished reactivity, drowsiness in a patient compared to the same amount of opioid alone.
19. The composition of claim 18, wherein the dopaminergic agent is L-DOPA, pramipexole, ropinirole, rotigotine, rasaligine, selegiline, tolcapone, entacapone, or a derivative, prodrug, or salt thereof.

20. The composition of claim 19, wherein the opioid is selected from the group consisting of fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, diacetylmorphine, methadone, alfentanil, buprenorphine, carfentanil, codeine, dezocine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, β-hydroxy-3-methylfentanyl, levomethadryl, levorphanol, lofentanil, meperidine, nalmefene, oxymorphone, pethidine, propoxyphene, sufentanil, tilidine, nalbuphine, pentazocine, butorphanol, derivatives, prodrugs, esters, and salts thereof.


Total Sedation Scores at Tmax vs. motor disability (MDS)
Sedation Score
MDS
R² = 0.7875
0
5
10
15
20
25
30
0
2
4
6
8
10
12
14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/34176

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/198; A61K 31/485; C07D 221/28 (2015.01)
CPC - C07D 221/28; A61K 31/198
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/198; A61K 31/485; C07D 221/28 (2015.01)
CPC: C07D 221/28; A61K 31/198

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/561; 514/567; 546/74

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar, PubWEST
opioid/opiate/narcotics, sedation/drowsiness, decrease/reduce/lower/attenuate, L-dopa/levodopa, dopaminergic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2012/149113 A1 (BRAITHWAITE et al.) 01 November 2012 (01.11.2012) pg 1, ln 9-11; pg 11, ln 1-22; pg 12, ln 7-10; pg 12, ln 25-27; pg 13, ln 1-6	1-12 --- 13-20
Y	WO 2012/089738 A1 (HOPP et al.) 05 July 2012 (05.07.2012) pg 19, ln 1-24	13, 18-20
Y	US 2011/0054038 A1 (GLOZMAN) 03 March 2011 (03.03.2011) para [0025]-[0026], [0068], [0153], [0158]-[0159], [0172]-[0173]	14-20
A	US 2003/0216413 A1 (ROOT-BERNSTEIN et al.) 20 November 2003 (20.11.2003) para [0029], [0031], [0101]	1-20
A	US 2013/0317035 A1 (DOLLE et al.) 28 November 2013 (28.11.2013) para [0563], [0655]-[0661]	1-20

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2015 (29.07.2015)	14 AUG 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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