mexiletine, sulfisoxazole and torasemide, or a salt, prodrug, derivative of any chemical purity, or sustained-release formulation thereof.

Preferred examples of drug combinations for use in the invention include, *e.g.*, baclofen and acamprosate, baclofen and cinacalcet, mexiletine and cinacalcet, torasemide and baclofen, or torasemide and sulfisoxazole. In a particular embodiment, the compositions and methods further comprise Levodopa.

One aspect of the invention relates to the use of a composition comprising acamprosate and cinacalcet, or salt(s) or sustained release formulation(s) thereof, in the manufacture of a medicament for use in the treatment of parkinsonism in a subject in need thereof.

Another aspect relates to a composition comprising: cinacalcet and acamprosate and levodopa, or cinacalcet and acamprosate and mexiletine and levodopa,or pharmaceutically acceptable salts thereof.

Another aspect relates to a composition comprising (i) cinacalcet, (ii) acamprosate and (iii) selegiline or rasagiline, or pharmaceutically acceptable salts or sustained release formulation(s) thereof.

The compositions in the invention may further comprise one or several pharmaceutically acceptable carrier(s) or excipient(s), and they may be administered repeatedly to the subject. Preferred compositions are administered orally. Moreover, the drugs may be formulated or administered together, separately or sequentially.

The invention is suitable for treating Parkinsonism in any mammalian subject, particularly in a human subject, at any stage of the disease. The invention may be used *e.g.*, to retard the development of the disease, to reduce, delay or prevent tremor, hypokinesia (*e.g.*, bradykinesia, akinesia, rigidity) postural instability, and/or pain, and/or to increase survival.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Effect of cinacalcet and mexiletine combination therapy against glutamate toxicity on neuronal cortical cells. The glutamate intoxication is significantly prevented by the combination of cinacalcet (64 pM) and mexiletine (25.6 pM) whereas, at those concentrations, cinacalcet and mexiletine alone have no significant effect on intoxication. *: $p<0.001$, significantly different from glutamate intoxication; (ANOVA + Dunnett Post-Hoc test).

Figure 2: Effect of sulfisoxazole and torasemide combination therapy against glutamate toxicity on neuronal cortical cells. The glutamate intoxication is significantly prevented by the combination of sulfisoxazole (6.8 nM) and torasemide (400 nM) whereas, at those concentrations, sulfisoxazole and torasemide alone have no significant effect on intoxication.*: $p<0.001$, significantly different from glutamate intoxication; (ANOVA + Dunnett Post-Hoc test).

CLAIMS

1. A composition for use in the treatment of Parkinsonism, comprising at least two compounds selected from acamprosate, baclofen, cinacalcet, mexiletine, sulfisoxazole and torasemide, or a salt, prodrug, derivative of any chemical purity, or sustained release formulation thereof.

2. The composition for use of claim 1, comprising at least one of the following drug combinations:

- baclofen and acamprosate,
- baclofen and cinacalcet,
- mexiletine and cinacalcet,
- torasemide and baclofen,
- torasemide and sulfisoxazole,
- baclofen and cinacalcet and mexiletine,
- cinacalcet and acamprosate and mexiletine,
- baclofen and acamprosate and cinacalcet,
- baclofen and acamprosate and torasemide,
- baclofen and acamprosate and mexiletine, or
- torasemide and baclofen and cinacalcet.

3. The composition of claim 1 or 2, for use for treating Parkinson's disease.

4. The composition for use of claim 3, further comprising levodopa, or a salt, prodrug, derivative of any purity, or sustained release formulation thereof.

5. The composition for use of any one of the preceding claims, which further comprises a pharmaceutically acceptable carrier or excipient.

6. The composition for use of any one of the preceding claims, wherein the compounds are formulated or administered together, separately or sequentially.

7. The composition for use of any one of the preceding claims, wherein said composition is administered repeatedly to the subject.

8. The composition for use of any one of the preceding claims, wherein said composition is administered orally.

9. The composition for use of any one of claims 1 to 7, wherein acamprosate, when present, is administered in a dosage of less than 50 mg per day, more preferably less than 10 mg per day.

10. The composition for use of any one of claims 1 to 8, wherein baclofen, when present, is administered in a dosage of less than 30 mg per day.

11. The composition of any one of claims 1 to 10, for use in protecting dopaminergic neurons of the nigrostriatal system from degeneration.

12. The composition of any one of claims 1 to 10, for use in the treatment of bradykinesia or akinesia.

13. A method of treating Parkinsonism in a mammalian subject in need thereof, the method comprising simultaneously, separately or sequentially administering to said subject an effective amount of a composition of any of the preceding claims.

14. The method of claim 13, wherein said subject in need thereof is also treated with deep brain stimulation of the subthalamic nucleus or of the *globus pallidus interna*.

15. The composition or method of any one of the preceding claims, for use in a preventive treatment in a subject in need thereof and at risk of Parkinsonism.

CLAIMS

1. Use of a composition comprising acamprosate and cinacalcet, or salt(s) or sustained release formulation(s) thereof, in the manufacture of a medicament for use in the treatment of parkinsonism in a subject in need thereof.

2. The use of claim 1, wherein said parkinsonism is a condition selected from Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, cortical-basal ganglionic degeneration, diffuse Lewy body disease, Parkinson's dementia, X-linked dystonia-parkinsonim, and secondary parkinsonism.

3. The use of claim 1, wherein said medicament is for treating Parkinson's disease.

4. The use according to claim 1, wherein said medicament comprises cinacalcet and acamprosate and mexiletine, or salt(s) or sustained release formulation(s) thereof.

5. The use according to claim 1 or 2, wherein the medicament further comprises at least one dopamine precursor, at least one dopamine receptor agonist, and/or at least one inhibitor of dopamine metabolizing enzymes.

6. The use according to claim 5, wherein the at least one dopamine precursor is selected from the group consisting of levodopa and melevodopa, or salts or sustained release formulations thereof, the at least one dopamine receptor agonist is selected from the group consisting of talipexole, piribedil, rotigotine, bromocriptine, pergolide, cabergoline, lisuride, pramipexole, ropinirole or apomorphine, or salts or sustained release formulations thereof, and the at least one inhibitor of dopamine metabolizing enzymes is selected from the group consisting of selegiline and rasagiline, or salts or sustained release formulations thereof.

7. The use according to claim 5 or 6, wherein the medicament comprises at least one of the following drug combinations:

- acamprosate, cinacalcet and levodopa, or

- acamprosate, cinacalcet, mexiletine and levodopa,
or salts or sustained release formulations thereof.

8. The use according to claim 7, wherein the medicament further comprises carbidopa or a salt or sustained release formulation thereof.

9. The use according to any one of the preceding claims, wherein the medicament further comprises a pharmaceutically acceptable carrier or excipient.

10. The use according to any one of the preceding claims, wherein the compounds are formulated or administered together, separately or sequentially.

11. The use according to any one of the preceding claims, wherein said medicament is to be administered repeatedly to the subject.

12. The use according to any one of the preceding claims, wherein said medicament is to be administered orally.

13. The use according to any one of claims 1 to 12, wherein acamprosate is provided in said medicament in a dosage of less than 50 mg per day, more preferably less than 10 mg per day.

14. The use according to any one of claims 1 to 13, wherein cinacalcet is provided in said medicament in a dosage of less than 100 mg per day, more preferably less than 36 mg per day.

15. The use according to any one of claims 1 to 14, for protecting dopaminergic neurons of the nigrostriatal system from degeneration.

16. The use according to any one of claims 1 to 14, for the treatment of bradykinesia or akinesia.

17. The use according to any one of the preceding claim, wherein said subject in need thereof is also treated with deep brain stimulation of the subthalamic nucleus or of the *globus pallidus interna*.

18. The use according to any one of the preceding claims, for preventive treatment in a subject in need thereof and at risk of parkinsonism.

19. The use according to any one of the preceding claims, wherein the subject is a human.

20. A composition comprising :
- cinacalcet and acamprosate and levodopa, or
- cinacalcet and acamprosate and mexiletine and levodopa,
or pharmaceutically acceptable salts thereof.

21. The composition of claim 20, further comprising at least one compound selected from carbidopa, benserazide, entocapone, tolcapone, selegiline and rasagiline, or pharmaceutically acceptable salts or sustained release formulation(s) thereof.

22. A composition comprising (i) cinacalcet, (ii) acamprosate and (iii) selegiline or rasagiline, or pharmaceutically acceptable salts or sustained release formulation(s) thereof.