aforementioned side effects, especially chronic side-effects, such as nephrotoxicity and chronic kidney disease. Thus, co-administration of gaboxadol and a sub-standard dose of lithium lowers the risks of side-effects and facilitates the management of bipolar disorder and other psychiatric disorders responsive to lithium treatment. In addition, a standard dose range of lithium (e.g. 600 to 1800 mg, with a daily maximum dose of 2400 mg) also synergizes or, in certain examples, acts additively, with gaboxadol, indicating that adding gaboxadol to a standard dose of lithium may prove useful for the augmentation of the response to lithium in treatment-resistant patients who do not initially respond to conventional lithium monotherapy.

There is provided a synergistic combination comprises gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds thereof.

In one aspect, there is provided a pharmaceutical composition comprising a synergistic combination of compounds present in synergistically effective amounts, wherein the synergistic combination is a combination consisting of gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds.

In certain examples, the lithium is given in a sub-standard dose range that when administered daily to a subject in need thereof is ineffective at treating bipolar disorder, depression, treatment-resistant depression and suicidality.

In certain examples, the lithium is given in a sub-standard dose range that when administered daily to a subject in need thereof, is below the medically recommended dose for treating bipolar disorder, depression, treatment-resistant depression, or suicidality.

In certain examples, an animal equivalent of the sub-standard dose of lithium is ineffective at activating c-fos signalling in an animal model's brain as measured by Pharmacomapping.

In preclinical testing, the sub-standard lithium human dose range can be established and differentiated from the standard dose range, for example, by mapping lithium-induced brain activation, represented by the visualization of the induction of the immediate early gene (IEG) *c-fos*, in an animal such a mouse or rat, or by recording lithium-induced changes in an animal's electroencephalogram (EEG).

In certain examples, the psychiatric disorder is chosen from bipolar disorder, depression, treatment-resistant depression or suicidality.

There is provided a pharmaceutical composition as provided above for use in therapy.

In another aspect, there is provided use of the pharmaceutical composition as provided above in the manufacture of a medicament for the treatment of a psychiatric disorder in a subject in need thereof.

In certain examples, the combination reduces at least one adverse side effect selected from the group consisting of nephrotoxicity, nephrogenic diabetes insipidus, chronic kidney disease, diarrhea, hand tremor, increased thirst, increased urination, vomiting, weight gain, impaired memory, poor concentration, drowsiness, muscle weakness, hair loss, acne and decreased thyroid function.

In certain examples, the combination reduces at least two adverse side effects selected from the group consisting of nephrotoxicity, nephrogenic diabetes insipidus, chronic kidney disease, diarrhea, hand tremor, increased thirst, increased urination, vomiting, weight gain, impaired memory, poor concentration, drowsiness, muscle weakness, hair loss, acne and decreased thyroid function

In certain examples, the combination reduces at least three adverse side effects selected from the group consisting of nephrotoxicity, nephrogenic diabetes insipidus, chronic kidney disease, diarrhea, hand tremor, increased thirst, increased urination, vomiting, weight gain, impaired memory, poor concentration, drowsiness, muscle weakness, hair loss, acne and decreased thyroid function

There is provided a method for treating a human diagnosed with bipolar disorder, depression, treatment-resistant depression or acute suicidality is disclosed that comprises administering a synergistic combination of gaboxadol at a dose ranging from about 5 to about 300 mg /day, contemporaneously with lithium at a dose from about 50 mg to about 1800 mg lithium carbonate, with a maximum daily dose of 2400 mg [for a 60kg human]; or from about 0.8 mg/kg to about 30 mg/kg, with a maximum dose of 40 mg/kg, of lithium carbonate; or in an amount

sufficient to achieve a lithium serum concentration of about 0.2 to 1.2 mmol/L; wherein the combination is administered at least once per day.

In another aspect, there is provided use of the pharmaceutical composition as provided above in the manufacture of a medicament for the treatment of bipolar disorder, depression, or acute suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 300 mg /day, and lithium a) at a dose in a range from 50 mg to 1800 mg lithium carbonate; or b) at a dose in a range from 0.8 mg/kg to 30 mg/kg lithium carbonate; wherein the medicament is to be administered at least once per day.

In another aspect, there is provided use of the pharmaceutical composition as provided herein in the manufacture of a medicament for the treatment of bipolar disorder, depression, or acute suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 300 mg/day, and lithium in an amount sufficient to achieve a lithium serum concentration of 0.2 mmol/L to 1.2 mmol/L; wherein the medicament is to be administered at least once per day.

There is provided a method for treating a human diagnosed with an acute form of bipolar disorder, depression, treatment-resistant depression or suicidality comprising administering a synergistic combination of gaboxadol at a dose in the range of from about 5 mg to about 150 mg/day, contemporaneously with lithium at a dose of from about 300 mg to about 1800 mg lithium

carbonate/day [for a 60kg human]; or in an amount sufficient to achieve a lithium serum concentration of 0.4 to 1.2 mmol/L, wherein the combination is administered at least once per day.

There is provided a method for treating a patient diagnosed with an acute form of bipolar disorder, depression, treatment-resistant depression or suicidality comprising administering a synergistic combination of gaboxadol at a dose in the range of from about 5 mg to about 150 mg/day, contemporaneously with lithium at a dose of from about 50 mg to about 900 mg lithium carbonate [for a 60kg human]; or in an amount sufficient to achieve a lithium serum concentration of about 0.2 to 1.0 mmol/L; wherein the combination dose is administered at least once per day.

There is provided a method for treating a patient diagnosed with an acute form of bipolar disorder, depression, treatment-resistant depression or suicidality comprising administering an additive combination of gaboxadol at a dose in the range of from about 5 mg to about 150 mg/day, contemporaneously with lithium at a dose from about 50 mg to about 900 mg lithium carbonate [for a 60kg human]; or in an amount sufficient to achieve a lithium serum concentration of about 0.2 to 1.0 mmol/L, wherein the combination dose is administered at least once per day.

In another aspect, there is provided use of the pharmaceutical composition as provided herein in the manufacture of a medicament for the treatment of an acute form of bipolar disorder, depression, or suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 50 mg/day and lithium at a dose in a range from 50 mg/day to 900 mg/day lithium carbonate; wherein the medicament is to be administered at least once per day.

In another aspect, there is provided use of the pharmaceutical composition as provided herein in the manufacture of a medicament for the treatment of an acute form of bipolar disorder, depression, or suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 50 mg/day and lithium in an amount sufficient to achieve a lithium serum concentration of 0.2 mmol/L to 1.0 mmol/L; wherein the medicament is to be administered at least once per day.

In another aspect, there is provided use of the pharmaceutical composition as provided herein in the manufacture of a medicament for the treatment of a chronic form of bipolar disorder, depression, or suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 30 mg/day and lithium at a dose in a range from 50 mg to 600 mg lithium carbonate; wherein the medicament is to be administered at least once per day.

In another aspect, there is provided use of the pharmaceutical composition as provided herein in the manufacture of a medicament for the treatment of a chronic form of bipolar disorder, depression, or suicidality in a subject in need thereof, wherein the gaboxadol or a salt thereof is to be administered at a dose in a range from 5 mg/day to 30 mg/day and lithium in an amount sufficient to achieve a lithium serum concentration of 0.2 mmol/L to 0.8 mmol/L; wherein the medicament is to be administered at least once per day.

In another aspect, there is provided use of the pharmaceutical composition as provided herein in the manufacture of a medicament for the treatment of a psychiatric disorder in a subject in need thereof, wherein: a) the lithium is to be administered in (i) a sub-standard daily dose of lithium in a range from 50 mg to 600 mg lithium carbonate per day; or (ii) a standard daily dose of lithium in a range from 600 mg to 1800 mg lithium carbonate per day; and/or b) the gaboxadol is to be administered in (i) a low daily dose of gaboxadol in a range from 5 mg to 15 mg per day, or a medium daily dose of gaboxadol in a range from 15 mg to 30 mg per day; or (ii) a high daily dose of gaboxadol in a range from 30 mg to 300 mg per day.

There is provided a use of gaboxadol and lithium in the preparation of a fixed dose combination medicament is disclosed, wherein the lithium is present in a range from about 10 mg to about 300 mg [lithium carbonate 50 mg to about 1800 mg]; and wherein the gaboxadol is present in a range from about 5 mg to about 150 mg for treatment of a human patient diagnosed with bipolar disorder, depression or acute suicidality.

There is provided a use of a fixed dose combination comprising lithium and gaboxadol in unit dosage form is disclosed wherein the lithium is present in a range from about 10 mg to about 360 mg [lithium carbonate 50 mg to about 1800 mg] and wherein the gaboxadol is present in a range from about 5 mg to about 150 mg for the treatment of a human patient diagnosed with bipolar disorder, depression or acute suicidality.

There is provided a use of a fixed dose combination comprising lithium and gaboxadol in unit dosage form for once daily administration is disclosed, wherein the gaboxadol is present from about 5 mg to about 150 mg, and the lithium for the first week is present in the range of from about 40 mg to about 360 mg [lithium carbonate 200 mg to about 1800 mg], and after the first week the lithium is present in the range of from about 10 mg to about 180 mg [lithium carbonate

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a synergistic combination of compounds present in synergistically effective amounts, wherein the synergistic combination is a combination consisting of gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds.

2. The pharmaceutical composition of claim 1, wherein the lithium is present in a sub-standard daily dose of lithium in a range from 50 mg to 600 mg lithium carbonate.

3. The pharmaceutical composition of claim 1, wherein the lithium is present in a standard daily dose of lithium in a range from 600 mg to 1800 mg lithium carbonate.

4. The pharmaceutical composition of any one of claims 1-3, wherein the gaboxadol is present in a low daily dose of gaboxadol in a range from 5 mg to 15 mg or a medium daily dose of gaboxadol in a range from 15 mg to 30 mg.

5. The pharmaceutical composition of any one of claims 1-3, wherein the gaboxadol is present in a high daily dose of gaboxadol in a range from 30 mg to 300 mg.

6. The pharmaceutical composition of any one of claims 1-5, wherein the pharmaceutical composition is in a form of a single tablet for oral consumption.

7. The pharmaceutical composition of any one of claims 1-6, wherein the pharmaceutical composition is in a form of a controlled release formulation.

8. The pharmaceutical composition of any one of claims 1-7, wherein the pharmaceutical composition further comprises one or more inert pharmaceutically acceptable excipients.

9. The pharmaceutical composition of any one of claims 1-8, wherein the pharmaceutical composition is in a form of a single dosage unit having separate compartments for the lithium and gaboxadol or the pharmaceutically acceptable salt of either or both compounds.

10. A kit comprising the pharmaceutical composition of any one of claims 1-9.

11. Use of the pharmaceutical composition of any one of claims 1-9 in the manufacture of a medicament for the treatment of a psychiatric disorder in a subject in need thereof.

12. The use of claim 11, wherein the psychiatric disorder is bipolar disorder, depression, treatment-resistant depression, or acute suicidality.

13. The use of claim 11 or 12, wherein animal equivalent doses of the lithium and gaboxadol in the amounts present in the pharmaceutical composition, when administered daily to an animal model are synergistically effective at activating *c-fos* signalling in at least one region of an animal model's brain selected from the group consisting of 1) a broad cortical activation comprising motor (MO), gustatory (GU), visceral (VISC), agranular insular (AI), somatosensory (SS), auditory, visual (VIS), auditory (AUD), prelimbic (PL) and infralimbic (ILA), retrosplenial (RSP), parietal (PTL), temporal associational (TEa), ectorhinal (ECT), entorhinal (ENT), perirhinal (PERI), piriform (PIR), and anterior cingulate (ACA) cortex, claustrum (CLA), as well as 2) subcortical activation comprising hippocampal CAI region, bed nuclei stria terminalis (BST), central amygdala (CEA), cortical amygdala (COA), basolateral and basomedial amygdala (BLA and BMA), medial amygdala (MEA), thalamic ventral posteromedial nucleus (VPM), subparafascicular nucleus (SPF), medial geniculate complex (MG), suprageniculate nucleus (SGN), nucleus of reunions (RE), rhomboid nucleus (RH), and central medial nucleus (CM) of a thalamus, paraventricular hypothalamic nucleus (PVH), dorsomedial nucleus of a hypothalamus (DMH), tuberomammillary nucleus (TM), parasubthalamic nucleus (PSTN) and subthalamic nucleus (STN), parabrachial nucleus, locus coeruleus (LC), and nucleus of a solitary tract (NTS).

14. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for the treatment of bipolar disorder, depression, or acute suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 300 mg /day, and lithium

    a) at a dose in a range from 50 mg to 1800 mg lithium carbonate; or

    b) at a dose in a range from 0.8 mg/kg to 30 mg/kg lithium carbonate;

    wherein the medicament is to be administered at least once per day.

15. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for the treatment of bipolar disorder, depression, or acute suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 300 mg/day, and lithium in an amount sufficient to achieve a lithium serum concentration of 0.2 mmol/L to 1.2 mmol/L;
wherein the medicament is to be administered at least once per day.

16. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for the treatment of an acute form of bipolar disorder, depression, or suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 50 mg/day and lithium at a dose in a range from 50 mg/day to 900 mg/day lithium carbonate;
wherein the medicament is to be administered at least once per day.

17. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for the treatment of an acute form of bipolar disorder, depression, or suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 50 mg/day and lithium in an amount sufficient to achieve a lithium serum concentration of 0.2 mmol/L to 1.0 mmol/L;
wherein the medicament is to be administered at least once per day.

18. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for the treatment of a chronic form of bipolar disorder, depression, or suicidality in a subject in need thereof, wherein the gaboxadol or salt thereof is to be administered at a dose in a range from 5 mg/day to 30 mg/day and lithium at a dose in a range from 50 mg to 600 mg lithium carbonate;
wherein the medicament is to be administered at least once per day.

19. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for the treatment of a chronic form of bipolar disorder, depression, or suicidality in a subject in need thereof, wherein the gaboxadol or a salt thereof is to be administered at a dose in a range from 5 mg/day to 30 mg/day and lithium in an amount sufficient to achieve a lithium serum concentration of 0.2 mmol/L to 0.8 mmol/L;

wherein the medicament is to be administered at least once per day.

20. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for the treatment of a psychiatric disorder in a subject in need thereof, wherein:

a) the lithium is to be administered in

(i) a sub-standard daily dose of lithium in a range from 50 mg to 600 mg lithium carbonate per day; or

(ii) a standard daily dose of lithium in a range from 600 mg to 1800 mg lithium carbonate per day; and/or

b) the gaboxadol is to be administered in

(i) a low daily dose of gaboxadol in a range from 5 mg to 15 mg per day, or a medium daily dose of gaboxadol in a range from 15 mg to 30 mg per day; or

(ii) a high daily dose of gaboxadol in a range from 30 mg to 300 mg per day.

21. The use of claim 20, wherein the treatment comprises a sub-standard daily dose of lithium to be administered in a range from 50 mg to 600 mg lithium carbonate per day.

22. The use of claim 20, wherein the treatment comprises a standard daily dose of lithium to be administered in a range from 600 mg to 1800 mg lithium carbonate per day.

23. The use of any one of claims 20-22, wherein the treatment comprises a low daily dose of gaboxadol to be administered in a range from 5 mg to 15 mg per day, or a medium daily dose of gaboxadol in a range from 15 mg to 30 mg per day.

24. The use of any one of claims 20-22, wherein the treatment comprises a high daily dose of gaboxadol to be administered in a range from 30 mg to 300 mg per day.

25. The use of any one of claims 11-24, wherein the subject is a human.