a significant risk of BD relapse. Clinical strategy in pregnancy is therefore to increase lithium dose during pregnancy, thereby achieving higher serum levels during the early postpartum period which is often associated with an increased risk of relapse (Deligiannidis et al., 2014). However, close monitoring of lithium serum levels is essential because as the patient's kidney function returns to a lower glomerular filtration rate during the postpartum period, the associated increase in serum lithium levels can cause acute toxicity in the mother as well as in the infant (Horton et al., 2012; Wesseloo et al., 2017).

Acute lithium toxicity can present as non-convulsive status epilepticus, slowing of EEG alpha rhythm, pathological 3–10 Hz delta rhythm and diffuse spike discharges, life-threatening coma, hypothonia and hyporeflexia (Ivkovic and Stern, 2014; Madhusudhan, 2014; Megarbane et al., 2014; Schou et al., 1968).

Additionally, chronic side-effects associated with long-term maintenance lithium treatment include hypothyroidism, nephrogenic diabetes insipidus and significant nephrotoxicity and chronic kidney disease especially in patients already diagnosed with kidney failure (Davis et al., 2018a; Davis et al., 2018b). In an epidemiological study that examined reasons for discontinuing lithium therapy amongst BD patients, the majority (62%) of people stopped taking lithium because of the adverse events, primarily renal disease, diarrhea and/or tremor (Öhlund et al., 2018). In 2014 alone, there were 6,850 reported cases of lithium toxicity in the United States. Lithium treatment therefore requires very careful monitoring and titration of serum lithium concentrations to achieve a long lasting therapeutic benefit.

Accordingly, there is an ongoing need for improved treatment options that mitigate the side effects associated with lithium treatment of many severe psychiatric disorders including bipolar disorder.

SUMMARY

This disclosure reports on the discovery that gaboxadol can act synergistically with lithium to enhance lithium's action on brain signaling activity. In particular, the combination of a sub-standard dose range of lithium (e.g. < 600 mg per day) with gaboxadol reduces the amount of lithium needed to treat psychiatric disorders, such as bipolar disorder (both in acute mania and long-term maintenance), depression, treatment resistant depression and suicidality without the

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 thereof.

fclaiIn 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 sub-standard dose of lithium is in the range from about 50 to about 600 mg lithium carbonate per day.

In certain examples, gaboxadol is given at a low to medium human dose range that, when given to an animal such as a mouse or rat at an animal equivalent dose

(AED), fails to evoke or evokes only a modest induction of c-fos activity in the brain as measured by Pharmacomapping.

In certain examples, the low dose of gaboxadol is in the range from about 5 to about 15 mg gaboxadol per day for an adult human and the medium dose of gaboxadol is in the range from about 15 to about 30 mg gaboxadol per day for an adult human.

In certain examples, the lithium is given at a standard dose range of lithium.

In certain examples, the standard dose range of lithium is in the range from about 600 to about 1800 mg, with a daily maximum dose of 2400 mg, of lithium carbonate per day for an adult human.

In certain examples, the gaboxadol is given as a high dose which, when given to an animal such as a mouse or rat at an animal equivalent dose (AED), evokes a strong induction of c-fos activity in the brain.

In certain examples, the high dose of gaboxadol is in the range from about 30 to about 300 mg gaboxadol per day for an adult human.

In certain examples, the amounts of lithium and gaboxadol administered daily to a subject in need thereof, are synergistically effective at inducing IEG *c-fos* signaling in at least one region of a subject's cortical brain selected from the group consisting of 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, and claustrum (CLA).

In certain examples, the amounts of lithium and gaboxadol administered daily to a subject in need thereof, are synergistically effective at inducing IEG *c-fos* signaling in at least two regions of a subject's cortical brain selected from the group consisting of 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, and claustrum (CLA).

In certain examples, the amounts of lithium and gaboxadol administered daily to a subject in need thereof, are synergistically effective at inducing IEG *c-fos* signaling in at least three regions of a subject's cortical brain selected from the group consisting of 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, and claustrum (CLA).

In certain examples, the amounts of lithium and gaboxadol administered daily to a subject in need thereof, are synergistically effective at inducing IEG *c-fos* signaling in at least one region of a subject's subcortical brain selected from the group consisting of hippocampal CA1 region, the 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 the thalamus, paraventricular hypothalamic nucleus (PVH), dorsomedial nucleus of the hypothalamus (DMH), tuberomammillary nucleus (TM), parasubthalamic nucleus (PSTN) and subthalamic nucleus (STN), parabrachial nucleus, locus coeruleus (LC), and nucleus of the solitary tract (NTS).

In certain examples, the amounts of lithium and gaboxadol administered daily to a subject in need thereof, are synergistically effective at inducing IEG *c-fos* signaling in at least two regions of a subject's subcortical brain selected from the group consisting of hippocampal CA1 region, the 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 the thalamus, paraventricular hypothalamic nucleus (PVH), dorsomedial nucleus of the hypothalamus (DMH), tuberomammillary nucleus (TM), parasubthalamic nucleus (PSTN) and subthalamic nucleus (STN), parabrachial nucleus, locus coeruleus (LC), and nucleus of the solitary tract (NTS).

In certain examples, the amounts of lithium and gaboxadol administered daily to a subject in need thereof, are synergistically effective at inducing IEG *c-fos* signaling in at least three regions of a subject's subcortical brain selected from the group consisting of hippocampal CA1 region, the 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 the thalamus, paraventricular hypothalamic nucleus (PVH), dorsomedial nucleus of the hypothalamus (DMH), tuberomammillary nucleus (TM), parasubthalamic nucleus (PSTN) and subthalamic nucleus (STN), parabrachial nucleus, locus coeruleus (LC), and nucleus of the solitary tract (NTS).

In certain examples, the amount of gaboxadol and lithium, when administered daily to a subject in need thereof, are synergistically effective at treating the subject's psychiatric disorder selected from the group consisting of bipolar disorder, depression, treatment resistant depression and suicidality.

In certain examples, the treatment of the subject's psychiatric disorder is effective at improving a score of at least one psychiatric rating scale specific for bipolar disorder, depression, treatment resistant depression or suicidality.

In certain examples, the gaboxadol and lithium, when administered to a subject diagnosed with depression, are synergistically effective at increasing the subject's Montgomery-Asberg Depression Rating Scale (MADRS) score.

In certain examples, the gaboxadol and lithium, when administered to a subject in need thereof, are synergistically effective at increasing a score of at least one psychiatric rating scale specific for bipolar disorder, depression, treatment resistant depression or suicidality.

In certain examples, the gaboxadol and lithium, when administered to a subject in need thereof, are synergistically effective at increasing a score of at least two psychiatric rating scales specific for bipolar disorder, depression, treatment resistant depression or suicidality.

In certain examples, the gaboxadol and lithium, when administered to a subject in need thereof, are synergistically effective at increasing a score of at least three psychiatric rating scales specific for bipolar disorder, depression, treatment resistant depression or suicidality.

In certain examples, the lithium, when administered daily to a subject in need thereof, is in an amount sufficient to maintain the serum level of lithium in the range of about 0.2 to about 1.2 mmol/L.

In certain examples, the lithium, when administered daily to a subject in need thereof, is in an amount sufficient to maintain the subject's serum level of lithium in the range of about 0.4 to about 0.8 mmol/L.

There is provided a pharmaceutical composition that comprises any one of the preceding examplesof the synergistic combination of lithium and gaboxadol.

In certain examples, the pharmaceutical composition is in the form of a single tablet for oral consumption.

In certain examples, the pharmaceutical composition is in a form of a controlled release formulation.

In certain examples, the pharmaceutical composition further comprises one or more inert pharmaceutically acceptable excipients.

In certain examples, the pharmaceutical composition is in the form of a single dosage unit having separate compartments for the lithium and gaboxadol or a pharmaceutically acceptable salt of either or both compounds thereof.

In another aspect, there is provided a kit that comprises any one of the preceding pharmaceutical compositions.

There is provided a method for treating a subject in need thereof comprising administering any one of the previous examples of the synergistic combination of lithium and gaboxadol.

In certain examples, the subject is diagnosed with a psychiatric disorder.

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

In another aspect, there is provided a pharmaceutical composition as provided above for use in therapy.

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

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 a synergistic combination of gaboxadol and lithium in the manufacture of a medicament for the treatment of bipolar disorder, depression, or acute suicidality, wherein the synergistic combination of gaboxadol is to be administered at a dose ranging from about 5 to about 300 mg /day, contemporaneously with lithium (a) at a dose from about 50 mg to about 1800 mg lithium carbonate; or (b) from about 0.8 mg/kg to about 30 mg/kg lithium carbonate; or (c) in an amount sufficient to achieve a lithium serum concentration of about 0.2 to 1.2 mmol/L; wherein the combination dose of gaboxadol and lithium 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 a synergistic combination of gaboxadol and lithium in the manufacture of a medicament for the treatment of an acute form of bipolar disorder, depression, or suicidality, wherein the synergistic combination of gaboxadol is to be administered at a dose in a range of from about 5 mg to about 50 mg/day, contemporaneously with lithium (a) at a dose of from about 50 mg to about 900 mg lithium carbonate/day; or (b) in an amount sufficient to achieve a lithium serum concentration of 0.2 to 1.0 mmol/L; wherein the combination dose of gaboxadol and lithium is to be administered at least once per day.

In another aspect, there is provided use of a synergistic combination of gaboxadol and lithium in the manufacture of a medicament for the treatment of a chronic form of bipolar disorder, depression, or suicidality, wherein the synergistic combination of gaboxadol is to be administered at a dose in a range of from about 5 mg to about 30 mg/day, contemporaneously with lithium (a) at a dose of from about 50 mg to about 600 mg lithium carbonate; or (b) in an amount sufficient to achieve a lithium serum concentration of about 0.2 to 0.8 mmol/L; wherein the combination dose of gaboxadol and lithium is to be administered at least once 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

50 mg to about 900 mg], for the treatment of a human patient diagnosed with bipolar disorder, depression or acute suicidality.

In another aspect, there is provided a use of a synergistic combination of gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds thereof, for reducing one or symptoms of bipolar disorder, depression, or suicidality.

In another aspect, there is provided a use of a synergistic combination of gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds thereof, in the manufacture of a medicament for reducing one or symptoms of bipolar disorder, depression, or suicidality.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows exemplary whole-brain pharmacomaps® representing drug-evoked brain activation in the mouse.

(A) Mice were treated with a drug or vehicle solution for the control group using either intraperitoneal (i.p.), per oral (p.o.). subcutaneous (s.c.), intramuscular (i.m.) or intravenous (i.v.) delivery.

(B) Treatment with the drug led to the induction of the immediate early gene c-fos expression in activated neurons that peaked within about 1.5 to about 3 hours depending on the drug's pharmacokinetics.

(C) After the aforementioned c-fos induction period, the mice were sacrificed and the c-fos induction was visualized using whole-brain immunostaining. The brains were then chemically cleared and imaged by light-sheet fluorescent microscopy (LSFM).

(D) The whole-brain scans are depicted as serial section datasets with an XYZ resolution of about 4 x 4 x 5 microns.

(E) The c-fos-positive cells were detected in these datasets using custom algorithms.

(F) The whole-brain distribution of the detected c-fos-positive cells was then represented in 3D as a spatial map of centroid points in the 3D space of the mouse brain.

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 thereof.

2. The pharmaceutical composition of claim 1, wherein the lithium is a sub-standard daily dose of lithium.

3. The pharmaceutical composition of claim 2, wherein the sub-standard dose of lithium, 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.

4. The pharmaceutical composition of claim 2, wherein 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.

5. The pharmaceutical composition of claim 2, wherein a human equivalent of the sub-standard dose of lithium is in a range from about 50 to about 600 mg lithium carbonate/day.

6. The pharmaceutical composition of claim 1, wherein the gaboxadol is a low to medium dose of gaboxadol.

7. The pharmaceutical composition of claim 6, wherein an animal equivalent of the low dose of gaboxadol is ineffective at activating c-fos signalling in an animal model's brain as measured by Pharmacomapping.

8. The pharmaceutical composition of claim 6, wherein a human equivalent of the low dose of gaboxadol is in a range from about 5 to about 15 mg gaboxadol/day.

9. The pharmaceutical composition of claim 6, wherein the medium dose of gaboxadol is in a range from about 15 to about 30 mg gaboxadol/day.

10. The pharmaceutical composition of claim 1, wherein the lithium is a standard dose of lithium.

11. The pharmaceutical composition of claim 10, wherein the standard dose of lithium is in a range from about 600 to about 1800 mg, with a maximum daily dose of 2400 mg, of lithium carbonate/day.

12. The pharmaceutical composition of claim 1, wherein the gaboxadol is a high dose of gaboxadol.

13. The pharmaceutical composition of claim 12, wherein an animal equivalent of the high dose of gaboxadol is effective at activating broad c-fos signalling in an animal model's brain.

14. The pharmaceutical composition of claim 12, wherein a human equivalent of the high dose of gaboxadol is in a range from about 30 to about 300 mg gaboxadol/day.

15. The pharmaceutical composition of any one of claims 1, 2, 6, 10 and 12, wherein animal equivalent doses of lithium and gaboxadol administered daily to an animal model in need thereof 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 CA1 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).

16. The pharmaceutical composition of any one of claims 1, 2, 6, 10 and 12, wherein the gaboxadol and lithium, when administered daily to a subject in need thereof, act synergistically to treat the subject's psychiatric disorder selected from the group consisting of bipolar disorder, depression, treatment resistant depression, and acute suicidality.

17. The pharmaceutical composition of claim 16, wherein the treatment of the subject's psychiatric disorder is effective at improving a score of at least one psychiatric rating scale specific for bipolar disorder, depression, treatment resistant depression, or suicidality.

18. The pharmaceutical composition of claim 1, wherein the gaboxadol and lithium, when administered to a subject diagnosed with bipolar depression, unipolar depression or treatment resistant depression are synergistically effective at increasing the subject's Montgomery-Asberg Depression Rating Scale (MADRS) score.

19. The pharmaceutical composition of claim 1, wherein the gaboxadol and lithium, when administered to a subject in need thereof, are synergistically effective at increasing a score of at least one psychiatric rating scale specific for bipolar disorder, depression, treatment resistant depression, or suicidality.

20. The pharmaceutical composition of claim 1, wherein the lithium, when administered daily to a subject in need thereof, is in an amount sufficient to maintain the subject's serum level of lithium in a range of about 0.4 to about 1.2 mmol/L.

21. The pharmaceutical composition of claim 2, wherein the lithium, when administered daily to a subject in need thereof, is in an amount sufficient to maintain the subject's serum level of lithium in a range of about 0.2 to about 0.8 mmol/L.

22. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in a form of a single tablet for oral consumption.

23. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in a form of a controlled release formulation.

24. The pharmaceutical composition of claim 1, further comprising one or more inert pharmaceutically acceptable excipients.

25. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in a form of a single dosage unit having separate compartments for the lithium and gaboxadol or a pharmaceutically acceptable salt of either or both compounds thereof.

26. A kit comprising the pharmaceutical composition of claim 1.

27. A pharmaceutical composition of any one of claims 1, 2, 6, 10 and 12 for use in therapy.

28. Use of a pharmaceutical composition of any one of claims 1, 2, 6, 10 and 12 in the manufacture of a medicament for the treatment of a psychiatric disorder.

29. The use of claim 28, wherein the psychiatric disorder is chosen from bipolar disorder, depression, treatment-resistant depression, or acute suicidality.

30. The use of claim 28, wherein the pharmaceutical composition reduces 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.

31. Use of a synergistic combination of gaboxadol and lithium in the manufacture of a medicament for the treatment of bipolar disorder, depression, or acute suicidality, wherein the synergistic combination of gaboxadol is to be administered at a dose ranging from about 5 to about 300 mg /day, contemporaneously with lithium

    a) at a dose from about 50 mg to about 1800 mg lithium carbonate; or
    b) from about 0.8 mg/kg to about 30 mg/kg lithium carbonate; or
    c) in an amount sufficient to achieve a lithium serum concentration of about 0.2 to 1.2 mmol/L;

    wherein the combination dose of gaboxadol and lithium is to be administered at least once per day.

32. Use of a synergistic combination of gaboxadol and lithium in the manufacture of a medicament for the treatment of an acute form of bipolar disorder, depression, or suicidality, wherein the synergistic combination of gaboxadol is to be administered at

a dose in a range of from about 5 mg to about 50 mg/day, contemporaneously with lithium

a) at a dose of from about 50 mg to about 900 mg lithium carbonate/day; or
b) in an amount sufficient to achieve a lithium serum concentration of 0.2 to 1.0 mmol/L;

wherein the combination dose of gaboxadol and lithium is to be administered at least once per day.

33. Use of a synergistic combination of gaboxadol and lithium in the manufacture of a medicament for the treatment of a chronic form of bipolar disorder, depression, or suicidality, wherein the synergistic combination of gaboxadol is to be administered at a dose in a range of from about 5 mg to about 30 mg/day, contemporaneously with lithium

a) at a dose of from about 50 mg to about 600 mg lithium carbonate; or
a) in an amount sufficient to achieve a lithium serum concentration of about 0.2 to 0.8 mmol/L;

wherein the combination dose of gaboxadol and lithium is to be administered at least once per day.

34. The use of a synergistic combination of gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds thereof, for reducing one or symptoms of bipolar disorder, depression, or suicidality.

35. The use of a synergistic combination of gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds thereof, in the manufacture of a medicament for reducing one or symptoms of bipolar disorder, depression, or suicidality.