None of the art described above addresses the urgent treatment of patients suffering from acute suicidality and treatment-resistant depression by administering a high dose (e.g., >50 mg per dose) gaboxadol once or intermittently every three days or more.

SUMMARY

Methods of reducing risk of suicide and/or achieving rapid relief of depression symptoms described herein include administering to a patient in need thereof an amount of gaboxadol or a pharmaceutically acceptable salt thereof sufficient to reduce the risk of suicide. Methods of reducing risk of suicide and achieving rapid relief from depression described herein include administering to a patient in need thereof a first single dose treatment of about 50 mg to about 300 mg gaboxadol or a pharmaceutically acceptable salt thereof wherein the first treatment provides improvement in the patient within 1 day and for 3 or more days after administration to the patient. No gaboxadol in any form is administered to the patient for 3 or more days following the first treatment after reaching a therapeutic effect threshold based on one or more clinical biomarkers, such as EEG or blood level of gaboxadol.

The first treatment of gaboxadol comprises an initial administration of gaboxadol or a pharmaceutically acceptable salt thereof and optionally, additional administration(s) of gaboxadol, or a pharmaceutically acceptable salt thereof, within 12 hours immediately following the initial administration. The optional second administration may be administered if a clinical test of the patient demonstrates insufficient response in the 160 minutes immediately after the first administration. In one example, the insufficient response is an EEG power density increase of less than 30% at the time point 160 minutes after the first administration. The EEG power density is preferably calculated in the 4.75-8.0 Hz range. Alternatively, the insufficient response may be a

pharmaceutically acceptable salts thereof. In certain examples, gaboxadol and ketamine are each provided at a synergistic dose, and may optionally be administered at the same time.

A method for reducing a risk of suicide and/or achieving a rapid-acting relief of depressive symptoms is disclosed comprising administering, a first treatment of gaboxadol, or pharmaceutically acceptable salt thereof, to a patient in need thereof in an amount sufficient to reduce the risk of suicide and/or to rapidly alleviate depressive symptoms, and optionally, administering a second treatment of gaboxadol, or pharmaceutically acceptable salt thereof, within less than 6 hours immediately following the administration of the first treatment, and if the patient experiences a recurrence of the risk of suicide and/or depressive symptoms, administering an additional treatment of gaboxadol, or pharmaceutically acceptable salt thereof, but not until at least 48 hours after the first treatment.

In one aspect, there is provided use of gaboxadol, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing a risk of suicide and/or achieving a rapid-acting relief of depressive symptoms, wherein a first treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is to be administered to a patient, and optionally, a second treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is to be administered within less than 6 hours immediately following the first treatment, and if the patient experiences a recurrence of the risk of suicide and/or depressive symptoms, an additional treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is to be administered but not until at least 48 hours after the first treatment.

In certain examples, the additional treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is administered at least every 3, 4, 5, 6 or 7 days after the administration of the first treatment.

In certain examples, the second treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is administered if a neurological test of the patient demonstrates an insufficient response within 180 minutes immediately after administration of the first treatment.

In certain examples, the insufficient response is an electroencephalogram (EEG) power density increase of less than 30% over baseline within 180 minutes after the first administration or a whole head magnetoencephalography (MEG) planar gradiometer increase of less +3 in a combined delta, theta and alpha activity within 180 minutes after the administration of the first treatment.

In certain examples, the electroencephalogram (EEG) power density is calculated in a 0.25-8.0 Hz range or in a 4.75-8.0 Hz range.

In certain examples, the electroencephalogram (EEG) power density is calculated in a Sigma (11.5-15.0 Hz), Beta-1 (15.5-20.0 Hz), Beta-2 (20.5-25.0 Hz) or Beta-3 (25.5-32.0 Hz) range.

In certain examples, the second treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is administered if a neurological test of the patient demonstrates an insufficient response within about 30, 60, 90 or 120 minutes immediately after administration of the first treatment.

In certain examples, the insufficient response is an electroencephalogram (EEG) power density increase of less than 30% over baseline within 180 minutes after the first administration or a whole head magnetoencephalography (MEG) planar gradiometer increase of less +3 in a combined delta, theta and alpha activity within about 30, 60, 90 or 120 minutes after the administration of the first treatment.

In certain examples, the method provides improvement in at least one symptom of risk of suicide selected from the group consisting of suicidal ideation, acute suicidality, recurrent thoughts of death, actions towards suicide and/or suicide attempts.

In certain examples, the patient is further diagnosed with a condition selected from among suicidal ideation, acute suicidality, risk of self-harm and/or treatment-resistant depression.

In certain examples, the patient has not been previously treated with, or is not currently being treated with, or is not responding to, an anti-depressive treatment.

In certain examples, the administration of the first treatment comprises about 1 mg to about 300 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In certain examples, the administration of the first treatment comprises about 33 mg to about 300 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In certain examples, the administration of the fi rst treatment comprises about 50 mg to about 300 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In certain examples, the administration of the first treatment comprises about 33 mg to about 150 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In certain examples, the administration of the first treatment comprises about 50 mg to about 150 mg gaboxadol or a pharmaceutically acceptable salt thereof.

In certain examples, the first treatment is administered in an oral dosage form.

In certain examples, the oral dosage form is an orally disintegrating form.

In certain examples, the first treatment is administered intranasally.

In certain examples, the administration of the first treatment of gaboxadol, or pharmaceutically acceptable salt thereof, results in a blood level that exceeds a $GABA_A$ receptor saturation level.

In certain examples, the $GABA_A$ receptor saturation level is a blood level greater than 900 ng/ml.

In certain examples, a patient's plasma level of gaboxadol achieves AUC_{0-2} of greater than about 900 ng*hr/ml after the administration of the first treatment.

In certain examples, a plasma T_{max} of gaboxadol is achieved within 45 minutes after administration of the first treatment.

In certain examples, the method further comprises administering to the patient, before, after or concurrently with the first treatment, any one of ketamine, SAGE-217, allopregnanolone, ganaxolone, alfadolone, alfaxolone, hydroxydione, minaxolone, pregnanolone, renanolone and other pregnane neurosteroids, AV-101 (L-4-Chlorokynurenine), rapastinel (GLYX-13), MGS0039, LY-341,495, MK-801 (dizocilpine), Ro 25-6981, rislenemdaz (CERC-301, MK-0657), apimostinel (NRX-1074), lanicemine (AZD6765), traxoprodil (CP-101606), (2R,6R)-hydroxynorketamine, decoglurant (INN) (RG1578, RO4995819), memantine, tiagabine, clozapine, [2-amino-4-(2,4,6-trimethylbenzylamino)-phenyl]-carbamic acid ethyl ester (AA29504) and pharmaceutically acceptable salts thereof.

In certain examples, the first treatment comprises administering concurrently a synergistic dose of gaboxadol, or pharmaceutically acceptable salt thereof, together with a synergistic dose of ketamine wherein the synergistic dose of gaboxadol, or pharmaceutically acceptable salt thereof, can be about 20mg or less and the synergistic dose of ketamine can be about 10mg or less.

In certain examples, the synergistic dose of gaboxadol, or pharmaceutically acceptable salt thereof, can be about 20mg, about 19mg, about 18mg, about 17mg, about 16mg, about 15mg, about 14mg, about 13 mg, about 12mg, about 11 mg, about l0mg, about 9mg, about 8mg, about 7mg, about 6mg, about 5mg, about 4mg, about 3 mg, about 2mg, about lmg or less.

In certain examples, synergistic dose of ketamine can be about 10 mg can be about 10 mg, about 9mg , about 8mg, about 7mg, about 6mg, about 5mg, about 4mg, about 3 mg, about 2mg, about 1mg or less.

A use of gaboxadol is disclosed for reducing risk of suicide in a patient at risk of suicide and/or for achieving fast-acting relief of depressive symptoms.

A use of gaboxadol is disclosed for the manufacture of a medicament for reducing risk of suicide in a patient at risk of suicide and/or achieving fast-acting relief of depressive symptoms.

BRIEF DESCRIPTION OF THE DRAWINGS

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

(A) Mice are 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) This leads to the induction of the immediate early gene c-fos in activated neurons that peaks typically within 1.5 to 3 hrs depending on the drug's pharmacokinetics.

(C) After that period the mice are killed, the c-fos induction is visualized using whole-brain immunostaining, the brains are chemically cleared and finally imaged by light-sheet fluorescent microscopy (LSFM).

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

CLAIMS

What is claimed is:

1. Use of gaboxadol, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing a risk of suicide and/or achieving a rapid-acting relief of depressive symptoms, wherein

    a first treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is to be administered to a patient, and

    optionally, a second treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is to be administered within less than 6 hours immediately following the first treatment, and

    if the patient experiences a recurrence of the risk of suicide and/or depressive symptoms, an additional treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is to be administered but not until at least 48 hours after the first treatment.

2. The use of claim 1, wherein the additional treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is to be administered at least every 3, 4, 5, 6 or 7 days after the administration of the first treatment.

3. The use of claim 1, wherein the second treatment of gaboxadol, or pharmaceutically acceptable salt thereof, is to be administered if a neurological test of the patient demonstrates an insufficient response within 180 minutes immediately after the first treatment.

4. The use of claim 3, wherein the insufficient response is an electroencephalogram (EEG) power density increase of less than 30% over baseline within 180 minutes after the first treatment.

5. The use of claim 4, wherein the electroencephalogram (EEG) power density is calculated in a 0.25-8.0 Hz range.

6. The use of claim 4, wherein the electroencephalogram (EEG) power density is calculated in a 4.75-8.0 Hz range.

7. The use of claim 3, wherein the insufficient response is a whole head magnetoencephalography (MEG) planar gradiometer increase of less +3 in a combined delta, theta and alpha activity within 180 minutes after the first treatment.

8. The use of claim 1, wherein the use provides improvement in at least one symptom of risk of suicide selected from the group consisting of suicidal ideation, acute suicidality, recurrent thoughts of death, actions towards suicide and/or suicide attempts.

9. The use of claim 1, wherein the patient is further diagnosed with a condition selected from among suicidal ideation, acute suicidality, risk of self-harm and/or treatment-resistant depression.

10. The use of claim 1, wherein the patient has not been previously treated with, or is not currently being treated with, or is not responding to, an anti-depressive treatment.

11. The use of claim 1, wherein the first treatment comprises about 1 mg to about 300 mg gaboxadol or a pharmaceutically acceptable salt thereof.

12. The use of claim 1, wherein the first treatment comprises about 33 mg to about 300 mg gaboxadol or a pharmaceutically acceptable salt thereof.

13. The use of claim 1, wherein the first treatment comprises about 50 mg to about 300 mg gaboxadol or a pharmaceutically acceptable salt thereof.

14. The use of claim 1, wherein the first treatment is to be administered in an oral dosage form.

15. The use of claim 14, wherein the oral dosage form is an orally disintegrating form.

16. The use of claim 1, wherein the first treatment is to be administered intranasally.

17. The use of claim 1, wherein the first treatment of gaboxadol, or pharmaceutically acceptable salt thereof, results in a blood level that exceeds a $GABA_A$ receptor saturation level.

18. The use of claim 17, wherein the $GABA_A$ receptor saturation level is a blood level greater than 900 ng/ml.

19. The use of claim 1, wherein a patient's plasma level of gaboxadol achieves AUC_{0-2} of greater than about 900 ng*hr/ml after the first treatment.

20. The use of claim 19, wherein a plasma T_{max} of gaboxadol is achieved within 45 minutes after the first treatment.

21. The use of claim 1, further comprising any one of ketamine, SAGE-217, allopregnanolone, ganaxolone, alfadolone, alfaxolone, hydroxydione, minaxolone, pregnanolone, renanolone and other pregnane neurosteroids, AV-101 (L-4-Chlorokynurenine), rapastinel (GLYX-13), MGS0039, LY-341,495, MK-801 (dizocilpine), Ro 25-6981, rislenemdaz (CERC-301, MK-0657), apimostinel (NRX-1074), lanicemine (AZD6765), traxoprodil (CP-101606), (2R,6R)-hydroxynorketamine, decoglurant (INN) (RG1578, RO4995819), memantine,

tiagabine, clozapine, [2-amino-4-(2,4,6-trimethylbenzylamino)-phenyl]-carbamic acid ethyl ester (AA29504) and pharmaceutically acceptable salts thereof, to be administered to the patient, before, after or concurrently with the first treatment.

22. The use of claim 1, wherein the first treatment comprises a synergistic dose of gaboxadol, or pharmaceutically acceptable salt thereof, to be administered concurrently together with a synergistic dose of ketamine.

23. The use of claim 23, wherein the synergistic dose of gaboxadol, or pharmaceutically acceptable salt thereof, is about 20mg or less.

24. The use of claim 23, wherein the synergistic dose of ketamine is about 10mg or less.