on this trial is found at Kasper et al (2012) Int J Neuropsychopharmacol. 2012 Jul;15(6):715-25. The trial did not test the effect of gaboxadol alone.

[0008] Gaboxadol (4,5,6,7-tetrahydroisoxazolo [5,4-c]pyridine-3-ol) (THIP)) is also described in EP Patent No. 0000338 EP 0840601, EP1641456, U.S. Patent Nos. 4,278,676, 4,362,731, 4,353,910, and WO 2005/094820, the contents of which are hereby incorporated by reference herein in their entireties.

[0009] Effects of deuteration are described in (Harbeson and Tung, 2014; Perrin and Dong, 2007; Perrin et al., 2005; Turowski et al., 2003). Binding isotope effects can contribute positively or negatively to a measured deuterium kinetic isotope effect (DIE) (Schramm, 2007; Schwartz and Schramm, 2009). These DIE changes are primarily due to the increase in energy required for the cleavage of the carbon-deuterium (C-D) covalent bond than the energy required to cleave the carbon-hydrogen (C-H) bond. The primary DIE can be expressed as kH/kD, the ratio of the rate of C-H vs. C-D bond-cleavage (Harbeson and Tung, 2014). Such DIE effect can be expected for example in drug metabolism by cytochrome P450s (CYPs) (Meunier et al., 2004). Gaboxadol is not metabolized by CYPs and the majority (84-93%) of the drug is excreted in the form of unchanged, unmetabolized drug and a glucuronic acid conjugate in urine (Schultz et al., 1981).

[0010] Citation of a reference, including publications, patents, and patent applications, herein shall not be construed as an admission that such reference is prior art to the present invention.

SUMMARY

[0011] Treatment of psychiatric disorders by administering compounds to patients in need of therapy requires compounds that are useful in eliciting favorable responses from patients. The use of deuterated gaboxadol addresses this need by providing a compound that elicits a higher response in the brain of patients compared to non-deuterated gaboxadol. Deuterated gaboxadol can be administered to patients along with additional compounds to provide additive or synergistic responses in patients.

[0012] The present disclosure provides gaboxadol that has deuterium present at ring carbon positions of the tetrahydro-pyridine ring of the molecule. Ring carbon deuterated d2-gaboxadol 7,7 and d6-gaboxadol are herein shown to elicit higher levels of brain activation in particular brain areas of interest than equivalent doses of non-deuterated gaboxadol as measured by whole brain activation studies in mice, thereby indicating for the first time that ring carbon deuterated gaboxadol may be a superior agent for treating psychiatric disorders.

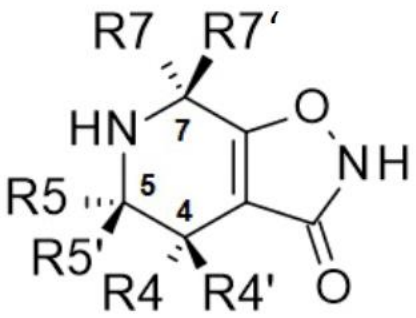
[0013] The present disclosure, as shown in the Examples, describes that the administration of

deuterated gaboxadol is a more pharmacologically effective treatment than an equivalent dose of gaboxadol and evokes a broad brain activation pattern which is very similar to ketamine, at lower doses than gaboxadol, with some key differences that are presumed to be related to a better safety profile of gaboxadol.

[0014] In addition, as shown in the Examples below, brain imaging in mice also shows additive and synergistic effects between gaboxadol and ketamine, suggesting that even though the drugs act at very different molecular targets, their downstream effect leads to a shared brain circuit-based mechanism.

[0015] For the purposes of the description herein, the terms “ring carbon deuterated gaboxadol” and “deuterated gaboxadol” and “deuterated gaboxadol compound” are used interchangeably to refer to forms of gaboxadol enriched with deuterium above the naturally occurring abundance of deuterium (i.e., deuterium occurs in place of hydrogen in all molecules in nature at approximately 0.0156%, the natural abundance of deuterium) and having deuterium atoms at one or more of the ring carbon positions of the tetrahydro-pyridine ring of gaboxadol (i.e., positions 4, 5 and 7).. Individual forms of deuterated gaboxadol including forms having 1 to 6 deuterium atoms are described below. In a specific example, the ring carbon deuterated gaboxadols of the present disclosure are synthesized to incorporate deuterium, at one or more of the 6 hydrogen positions associated with the ring carbons of the tetrahydro-pyridine ring of gaboxadol, for example, by any of the methods provided herein or using processes known in the art.

[0015a] In one aspect, the present disclosure provides a ring carbon deuterated gaboxadol compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof,

wherein R4, R4', R5, R5', R7 and R7' are independently H or D,

wherein D is present at five or more of R4, R4', R5, R5', R7 and R7', and

wherein the ring carbon deuterated gaboxadol compound is enriched with deuterium above the naturally occurring abundance of deuterium.

[0015b] In another aspect, the present disclosure provides a method of making d6-gaboxadol, said method comprising:

(a) treating 3-hydroxypyridine-4-carboxylic acid with deuterium oxide under catalytic hydrogenation conditions to provide 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylic acid;

(b) treating 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylic acid from step (a) above with a methylating agent to provide methyl 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylate;

(c) treating methyl 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylate from step (b) above with hydroxylamine hydrochloride to provide 2,3,6-trideuterio-5-hydroxy-pyridine-4-carbohydroxamic acid;

(d) treating 2,3,6-trideuterio-5-hydroxy-pyridine-4-carbohydroxamic acid from step (c) above with an activating agent to provide 4,5,7-trideuterioisoxazolo[5,4-c]pyridin-3-one;

(e) treating 4,5,7-trideuterioisoxazolo[5,4-c]pyridin-3-one from step (d) above with a brominating agent to provide 6-benzyl-4,5,7-trideuterio-isoxazolo[5,4-c]pyridin-6-ium-3-ol bromide;

(f) treating 6-benzyl-4,5,7-trideuterio-isoxazolo[5,4-c]pyridin-6-ium-3-ol bromide from step (e) above with a reducing agent to provide 6-benzyl-4,4,5,5,7,7-hexadeuterio-isoxazolo[5,4-c]pyridin-3-ol; and

(g) deprotecting 6-benzyl-4,4,5,5,7,7-hexadeuterio-isoxazolo[5,4-c]pyridin-3-ol from step (f) above to remove the benzyl group to provide d6-gaboxadol.

[0016] The disclosure provides methods of treating a psychiatric disorder by administering to a patient in need thereof a pharmaceutical composition comprising a therapeutically effective amount of deuterated gaboxadol or a pharmaceutically acceptable salt thereof, in a specific example administering about 1 mg to about 300 mg of deuterated gaboxadol or a pharmaceutically acceptable salt thereof.

[0017] The therapeutic examples of this disclosure include a method of treatment comprising administering deuterated gaboxadol. As used herein, treatment and therapy can be interchangeable. A course of therapy can include a first administration of deuterated gaboxadol and an additional administration or multiple additional administrations of deuterated gaboxadol. In this type of course of therapy, as used herein, the initial administration can be referred to as a prior administration and the additional administration(s) can be referred to as a subsequent administration(s). As used herein, a "first administration" or "initial administration" or "prior administration" can be used interchangeably, and also can

be referred to as a “prior administration” when a subsequent administration is contemplated. Herein, “additional administration” or “subsequent administration” can be used interchangeably.

[0018] A specific example of the disclosure provides methods of treating a psychiatric disorder (in a particular example, reducing risk of suicide and/or treating depression, e.g., achieving rapid relief of depression or one or more depression symptoms) comprising administering to a patient in need thereof an effective amount of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, sufficient to treat the psychiatric disorder, to reduce the risk of suicide and/or to treat the depression (e.g.,by achieving relief of one or more depression symptoms). The deuterated gaboxadol of the present disclosure can be administered alone or in combination with other drugs.

[0019] A specific example of the disclosure is a method of treating a psychiatric disorder (in a particular example, reducing risk of suicide and/or treating depression, e.g, achieving rapid relief of depression or one or more symptoms of depression) comprising administering to a patient in need thereof a single dose treatment of about 1 mg to about 300 mg, and preferably 1 mg to about 200 mg, and more preferably 50 mg to 100 mg deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, wherein the treatment provides improvement in the patient within 1 day.

[0020] In a specific example, the method of treating is to achieve rapid relief or rapid onset of treatment effect of the psychiatric disorder , e.g. of one or more symptoms of the psychiatric disorder, where rapid relief, rapidly alleviate or rapid onset of treatment effect is relief or onset of treatment effect within 24 hours or 12 hours or 6 hours or 2 hours after administering the deuterated gaboxodal to the patient.

[0021] In a particular example, the method of treatment comprises performing an initial administration of deuterated gaboxadol or a pharmaceutically acceptable salt thereof and optionally, additional administration(s) of deuterated gaboxadol, where an additional, subsequent administration is done within about 12 hours immediately following the prior, initial administration, preferably within about 6 hours, and most preferably within about 180 minutes of the initial administration. The optional second administration, sometimes referred to as a subsequent 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 about 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 whole head MEG planar gradiometer increase of less +3 in the combined delta, theta and alpha activity at the time point about 160 minutes after the first administration. The additional administration comprises deuterated gaboxadol up to the remainder of the maximum total first dose of 200 - 300 mg. Insufficient response may also mean failure to achieve a specified blood level of gaboxadol.

[0022] In certain examples, the method of treatment comprises performing an initial administration of deuterated gaboxadol or a pharmaceutically acceptable salt thereof and optionally performing additional administration(s) of non-deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, within about 12 hours immediately following the initial administration of deuterated gaboxadol, preferably within about 6 hours, and most preferably within about 180 minutes of the initial administration, if an insufficient response is noted.

[0023] In certain examples, the method of treatment comprises performing an initial administration of gaboxadol or a pharmaceutically acceptable salt thereof and optionally performing an additional administration(s) of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, within about 12 hours immediately following the initial administration of gaboxadol, if an insufficient response is noted.

[0024] In a specific example, provided is a method for reducing an imminent risk of suicide in a patient suffering from acute suicidality comprising administering a single dose of 10 to 200 mg deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, to the patient, optionally wherein the dose reduces the incidence of suicidal ideation within about 24 hours of the administration.

[0025] In a specific example, provided is a method of treating a psychiatric disorder, e.g, reducing risk of suicide or achieving a rapid relief from depression, comprising administering to a patient in need thereof a first pharmaceutical composition comprising deuterated gaboxadol or a pharmaceutically acceptable salt thereof and a second pharmaceutical composition comprising ketamine, SAGE-217, tiagabine, clozapine, and/or gaboxadol and pharmaceutically acceptable salts thereof. The second pharmaceutical composition can be administered concurrently, contemporaneously or sequentially.

[0026] In certain examples, deuterated gaboxadol and ketamine are each provided at a synergistic dose and may be administered contemporaneously, concurrently, or sequentially, and in the same or separate pharmaceutical compositions.

[0027] A specific example of the disclosure is a therapy for reducing a risk of suicide and/or treating depression, e.g., achieving a rapid relief of depression or one or more symptoms of depression, comprising performing a first administration of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, to a patient in need thereof in an amount sufficient to reduce the risk of suicide and/or to treat depression, e.g., to rapidly alleviate depressive symptoms, and optionally, performing an additional administration(s) of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, within less than about 6 hours immediately following the first administration, and if the patient experiences a recurrence of the risk of suicide and/or depressive symptoms, performing additional administration(s).

[0028] In certain examples, the first administration comprises administration of gaboxadol, or a pharmaceutically acceptable salt thereof, and the additional administration(s) comprises the administration of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof.

[0029] In certain examples, the first administration comprises administration of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, and the additional administration(s) comprises the administration of gaboxadol, or a pharmaceutically acceptable salt thereof.

[0030] In certain examples, one or more additional administrations are provided at 1, 2, 3, 4, 5, 6 or 7 days after the first administration.

[0031] In certain examples, the optional second or additional administration is performed if a neurological test of the patient demonstrates an insufficient response within about 180 minutes immediately after the first administration.

[0032] In certain examples, the insufficient response is an electroencephalogram (EEG) power density increase of less than 30% over baseline within about 180 minutes after the first administration or a whole head magnetoencephalography (MEG) planar gradiometer increase of less than +3 in a combined delta, theta and alpha activity within about 180 minutes after the first administration.

[0033] 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.

[0034] 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.

[0035] In certain examples, the optional second or additional administration(s) of deuterated gaboxadol, gaboxadol, or a pharmaceutically acceptable salt thereof, is performed if a

neurological test of the patient demonstrates an insufficient response within about 30, about 60, about 90 or about 120 minutes immediately after the first administration.

[0036] In certain examples, the insufficient response is an electroencephalogram (EEG) power density increase of less than 30% over baseline within about 180 minutes after the first administration or a whole head magnetoencephalography (MEG) planar gradiometer increase of less than +3 in a combined delta, theta and alpha activity within about 30, about 60, about 90 or about 120 minutes after the first administration.

[0037] In certain examples, the method provides improvement in at least one symptom of risk of suicide, wherein the symptom can be, but is not limited to suicidal ideation, acute suicidality, recurrent thoughts of death, action(s) towards suicide, suicide attempt(s), risk of self-harm and/or treatment-resistant depression.

[0038] 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.

[0039] In certain examples, the first and/or an additional administration comprises about 1 mg to about 300 mg, preferably about 1 mg to about 200 mg, deuterated gaboxadol or a pharmaceutically acceptable salt thereof.

[0040] In certain examples, the first and/or an additional administration comprises about 1 mg to about 300 mg deuterated gaboxadol or a pharmaceutically acceptable salt thereof.

[0041] In certain examples, the first and/or an additional administration comprises about 1 mg to about 20 mg deuterated gaboxadol or a pharmaceutically acceptable salt thereof.

[0042] In certain examples, the first and/or an additional administration comprises about 5 mg to about 10 mg deuterated gaboxadol or a pharmaceutically acceptable salt thereof.

[0043] In certain examples, the first and/or an additional administration comprises about 50 mg, 75 mg or 100 mg deuterated gaboxadol or a pharmaceutically acceptable salt thereof.

[0044] In certain examples, the first and/or an additional administration is of an oral dosage form. In certain examples, the oral dosage form is an orally disintegrating form.

[0045] In certain examples, the first and/or an additional administration is performed intranasally.

[0046] In certain examples, a plasma Tmax of deuterated gaboxadol is achieved within 45 minutes after the first administration.

[0047] In certain examples, the method further comprises additionally administering to the patient,

before, after or concurrently with the first administration, any one of: lithium, ketamine, AXS-05 (fixed combination of dextromethorphan and bupropion), SAGE-217, allopregnanolone, ganaxolone, alfadolone, alfaxolone, hydroxydione, minaxolone, pregnanolone, renanolone, 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, and [2-amino-4-(2,4,6-trimethylbenzylamino)-phenyl]-carbamic acid ethyl ester (AA29504), and a pharmaceutically acceptable salt of any of the foregoing.

[0048] In certain examples, the therapy comprises administering in combination a dose of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, together with a dose of a second pharmaceutical agent, wherein the dose of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, is about 20 mg or less, and the effect of the combination is additive or synergistic with respect to administration of the agents separately and not in combination.

[0049] In certain examples, the therapy comprises concurrently administering a synergistic dose of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, together with a synergistic dose of ketamine wherein the synergistic dose of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, is about 20 mg or less and the synergistic dose of ketamine is about 10 mg or less.

[0050] In certain examples, the synergistic dose of deuterated gaboxadol, or a pharmaceutically acceptable salt thereof, is about 20 mg, about 19 mg, about 18 mg, about 17 mg, about 16 mg, about 15 mg, about 14 mg, about 13 mg, about 12 mg, about 11 mg, about 10 mg, about 9 mg, about 8 mg, about 7 mg, about 6 mg, about 5 mg, about 4 mg, about 3 mg, about 2 mg, about 1 mg or less.

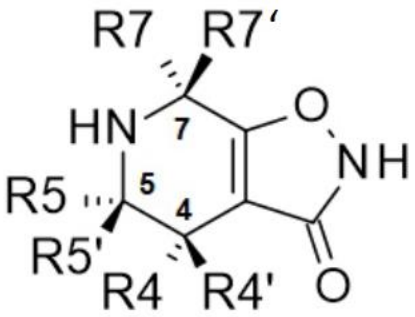
[0051] In certain examples, a synergistic dose of ketamine is about 10 mg, about 9 mg, about 8 mg, about 7 mg, about 6 mg, about 5 mg, about 4 mg, about 3 mg, about 2 mg, about 1 mg or less than about 1 mg.

[0052] In certain examples, provided herewin is a use of deuterated gaboxadol alone for the manufacture of a medicament for the treatment of a psychiatric disorder including but not limited to reducing risk of suicide in a patient at risk of suicide, treatment resistant depression and/or rapidly alleviate depressive symptoms.

[0053] This disclosure includes methods and compositions wherein deuterated 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 deuterated gaboxadol is believed to reduce 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 potentially without the aforementioned side effects, especially chronic side-effects, such as nephrotoxicity and chronic kidney disease. Thus, co-administration of deuterated gaboxadol and a sub-standard dose of lithium lowers the risks of side-effects and is expected to facilitate the management of bipolar disorder and other psychiatric disorders responsive to lithium treatment. In addition, a standard dose range of lithium (e.g. 600 mg to 1800 mg, with a daily maximum dose of 2400 mg) also is believed to synergize or, in certain examples, to act additively, with deuterated gaboxadol, indicating that adding deuterated 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.

[0053a] In another aspect, the present disclosure provides a composition comprising ring carbon deuterated gaboxadol compounds of Formula I



(I)

or a pharmaceutically acceptable salt thereof,

wherein R4, R4', R5, R5', R7 and R7' are independently H or D,

and wherein:

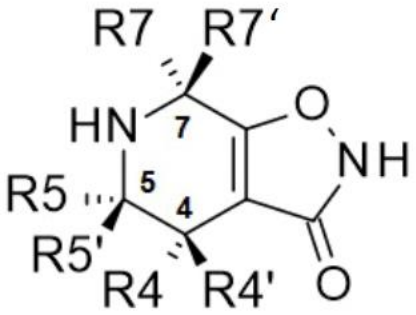
at least 50% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at all of R4, R4', R5, R5', R7 and R7'; or

at least 50% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at five positions selected from the group consisting of R4, R4', R5, R5', R7 and R7'.

[0053b] In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound or salt as described herein or the composition as described herein, and a pharmaceutically acceptable carrier.

[0053c] In another aspect, the present disclosure provides a pharmaceutical composition, wherein the pharmaceutical composition comprises:

(a) a ring carbon deuterated gaboxadol compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof,

wherein R4, R4', R5, R5', R7 and R7' are independently H or D, and

wherein D is present at five or more of R4, R4', R5, R5', R7 and R7; and

(b) lithium or a pharmaceutically acceptable salt of lithium,

wherein the ring carbon deuterated compound is enriched with deuterium above the naturally occurring abundance of deuterium.

[0054] In this disclosure, a synergistic combination comprises deuterated gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds thereof.

[0055] In certain examples, provided herein is a synergistic combination in a pharmaceutical composition comprising deuterated gaboxadol another compound, such as lithium, or a pharmaceutically acceptable salt of either or both compounds thereof and a pharmaceutically acceptable carrier.

[0056] In certain examples, provided herein is a synergistic combination that is a pharmaceutical composition comprising deuterated gaboxadol, or a pharmaceutically acceptable salt thereof and a second pharmaceutical composition comprising lithium, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0057] In certain examples, wherein deuterated gaboxadol and lithium are given in combination, the lithium is given in a sub-standard dose that when administered daily to a subject in need thereof is ineffective at treating bipolar disorder, depression, treatment-resistant depression or suicidality.

[0058] In certain examples, wherein deuterated gaboxadol and lithium are given in combination, the lithium is given in a sub-standard dose 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.

[0059] In certain examples, wherein deuterated gaboxadol and lithium are given in combination, the

lithium is given in a dose that is an animal equivalent of a sub-standard dose of lithium that is ineffective at activating c-fos signaling in an animal model's brain as measured by Pharmacomapping.

[0060] 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).

[0061] In certain examples of the above, the sub-standard dose of lithium is in the range from about 50 to about 600 mg lithium carbonate per day.

[0062] In certain examples of the above, deuterated gaboxadol is given at a human dose 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 low or moderate induction of c-fos activity in the brain as measured by Pharmacomapping. In a specific example, low induction of c-fos activity in the brain is indicated by activation of one to two cortical areas, such as anterior cingulate (ACA) and retrosplenial (RSP) cortex and/or one to three subcortical areas, such as bed nuclei stria terminalis (BST), central amygdala (CEA), and locus coeruleus (LC). In a specific example, moderate induction of c-fos activity in the brain is indicated by activation of three to six cortical areas, such as ACA, RSP, gustatory (GU), visceral (VISC), auditory (AUD) and visual (VIS) cortex and/or four to six subcortical areas, such as BST, CEA, LC, nucleus of reunions (RE), romboid nucleus (RH) and central medial nucleus (CM) of the thalamus.

[0063] In certain examples of the above, the dose of deuterated gaboxadol administered is in the range from about 1 to about 15 mg, about 15 to about 30 mg, or about 30 to about 300 mg deuterated gaboxadol per day for an adult human.

[0064] In certain examples of the above, the lithium is given at a standard dose of lithium.

[0065] In certain examples of the above, 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.

[0066] In certain examples of the above, the deuterated gaboxadol is given as a 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 a specific example, strong induction of c-fos activity in the brain is indicated by activation of more than 6 cortical areas, such as

ACA, RSP, GU, VISC, AUD, VIS, motor (MO), agranular insular (AI), somatosensory (SS), prelimbic (PL) and infralimbic (ILA), parietal (PTL), temporal associational (TEa), ectorhinal (ECT), entorhinal (ENT), perirhinal (PERI), and piriform (PIR) cortex and claustrum (CLA) and/or more than 6 subcortical areas, such as BST, CEA, LC, RE, RH, CM, hippocampal CA1 region, 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), paraventricular hypothalamic nucleus (PVH), dorsomedial nucleus of the hypothalamus (DMH), tuberomammillary nucleus (TM), parasubthalamic nucleus (PSTN) and subthalamic nucleus (STN), parabrachial nucleus, and nucleus of the solitary tract (NTS).

[0067] In certain examples of the above, the amounts of lithium and deuterated 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).

[0068] In certain examples of the above, the amounts of lithium and deuterated 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).

[0069] In certain examples of the above, the amounts of lithium and deuterated 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).

[0070] In certain examples of the above, the amounts of lithium and deuterated 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).

[0071] In certain examples of the above, the amounts of lithium and deuterated 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).

[0072] In certain examples of the above, the amounts of lithium and deuterated 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).

[0073] In certain examples of the above, the amount of deuterated gaboxadol another compound, such as 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.

[0074] In certain examples of the above, 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.

[0075] In certain examples of the above, the deuterated gaboxadol another compound, such as lithium, when administered to a subject diagnosed with depression, are synergistically effective at increasing the subject's Montgomery-Asberg Depression Rating Scale (MADRS) score.

[0076] In certain examples of the above, the deuterated gaboxadol another compound, such as 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.

[0077] In certain examples of the above, the deuterated gaboxadol another compound, such as 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.

[0078] In certain examples of the above, the deuterated gaboxadol another compound, such as 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.

[0079] In certain examples of the above, 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.

[0080] In certain examples of the above, 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.

[0081] In this disclosure, a pharmaceutical composition is disclosed that comprises any one of the preceding examples of the synergistic combination of lithium and deuterated gaboxadol.

[0082] In certain examples of the above, the pharmaceutical composition is in the form of a single tablet for oral consumption.

[0083] In certain examples of the above, the pharmaceutical composition is in a form of a controlled release formulation.

[0084] In certain examples of the above, the pharmaceutical composition is in a form of an oral dose formulation.

[0085] In certain examples of the above, the pharmaceutical composition further comprises one or more inert pharmaceutically acceptable excipients.

[0086] In certain examples of the above, the pharmaceutical composition is in the form of a single dosage unit having separate compartments for the lithium and deuterated gaboxadol or a pharmaceutically acceptable salt of either or both compounds thereof.

[0087] A kit is disclosed that comprises any one of the preceding pharmaceutical compositions.

[0088] A method is disclosed for treating a subject in need thereof comprising administering any one of the previous examples of the synergistic combination of lithium and deuterated gaboxadol.

[0089] In certain examples of the above, the subject is diagnosed with a psychiatric disorder.

[0090] In certain examples of the above, the psychiatric disorder is chosen from bipolar disorder, depression, treatment-resistant depression or suicidality.

[0091] In certain examples of the above, 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.

[0092] In certain examples of the above, 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.

[0093] In certain examples of the above, 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.

[0094] 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 deuterated gaboxadol at a dose ranging from about 1 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.

[0095] 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 deuterated gaboxadol at a dose in the range of from about 1 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.

[0096] 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 deuterated gaboxadol at a dose in the range of from about 1 mg to about 150 mg/day, contemporaneously with lithium at a dose of from about 50 mg to about 900 mg lithium carbonate [e.g., 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.

[0097] 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 deuterated gaboxadol at a dose in the range of from about 1 mg to about 150 mg/day, contemporaneously with lithium at a dose from about 50 mg to about

900 mg lithium carbonate [e.g., 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.

[0097a] In another aspect, the present disclosure provides use of the compound as described herein or the composition as described herein, in the manufacture of a medicament for treating a psychiatric disorder.

[0097b] In another aspect, the present disclosure provides use of a combination of a ring carbon deuterated gaboxadol compound and lithium, or a pharmaceutically acceptable salt of the compound or lithium or both, in the manufacture of a medicament for treating a psychiatric disorder, wherein the compound is enriched with deuterium above the naturally occurring abundance of deuterium.

[0098] A use of deuterated 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 [optionally in the form of lithium carbonate 50 mg to about 1800 mg]; and wherein the deuterated gaboxadol is present in a range from about 1 mg to about 150 mg for treatment of a human patient diagnosed with bipolar disorder, depression or acute suicidality.

[0099] A use of a fixed dose combination comprising lithium and deuterated gaboxadol in unit dosage form is disclosed wherein the lithium is present in a range from about 10 mg to about 360 mg [optionally in the form of lithium carbonate 50 mg to about 1800 mg] and wherein the deuterated gaboxadol is present in a range from about 1 mg to about 150 mg for the treatment of a human patient diagnosed with bipolar disorder, depression or acute suicidality.

[0100] A use of a fixed dose combination comprising lithium and deuterated gaboxadol in unit dosage form for once daily administration is disclosed, wherein the deuterated gaboxadol is present from about 1 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 [optionally in the form of 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 [optionally in the form of

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

[0101] A use of a synergistic combination of deuterated gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds thereof, is disclosed for reducing one or symptoms of bipolar disorder, depression, or suicidality.

[0102] A use of a synergistic combination of deuterated gaboxadol and lithium, or a pharmaceutically acceptable salt of either or both compounds thereof, is disclosed in the manufacture of a medicament for reducing one or symptoms of bipolar disorder, depression, or suicidality.

[0103] This disclosure provides deuterated gaboxadol having at least one deuterium present at a ring carbon of the tetrahydro-pyridine ring of gaboxadol.

[0104] This disclosure provides ring carbon deuterated gaboxadol with deuterium at all 6 ring

carbon hydrogen positions of the tetrahydro-pyridine ring of gaboxadol.

[0105] This disclosure provides deuterated gaboxadol with deuterium at 5 of the 6 ring carbon hydrogen positions of the tetrahydro-pyridine ring of gaboxadol.

[0106] This disclosure provides deuterated gaboxadol with deuterium at 3 of the 6 ring carbon hydrogen positions of the tetrahydro-pyridine ring of gaboxadol.

[0107] This disclosure provides deuterated gaboxadol with deuterium at ring carbon hydrogen positions 5,5,7,7 of the tetrahydro-pyridine ring of gaboxadol.

[0108] This disclosure provides deuterated gaboxadol made by one of the synthetic schemes disclosed herein.

[0109] This disclosure provides the use of deuterated gaboxadol for the manufacture of a medicament for the treatment of psychiatric disorders including but not limited to reducing risk of suicide in a patient at risk of suicide, treatment resistant depression and/or achieving fast-acting relief of depressive symptoms.

BRIEF DESCRIPTION OF THE DRAWINGS

[0110] **Figure 1A** shows the d1-gaboxadol form has 6 potential species.

[0111] **Figure 1B** shows the d2-gaboxadol form has 15 potential species.

[0112] **Figure 1C** shows the d3-gaboxadol form has 20 potential species.

[0113] **Figure 1D** shows the d4-gaboxadol form has 15 potential species.

[0114] **Figure 1E** shows the d5-gaboxadol form has 6 potential species.

[0115] **Figure 1F** shows that d6-gaboxadol has only one species.

[0116] **Figure 2** shows forms of deuterated gaboxadol and the ring numbering system

[0117] **Figure 3** shows a schema for the synthesis of 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-7,7-d2-3-ol (d2-gaboxadol 7,7).

[0118] **Figure 4** shows the distribution of forms of deuterated gaboxadol in the composition of Example 1B. 91% of the deuterated gaboxadol in the composition was in the form of d2-gaboxadol-7,7 according to calculation from the raw data of peak intensity and abundance.

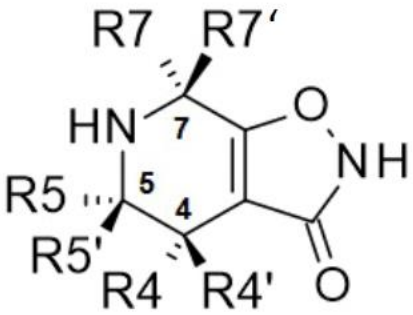
[0119] **Figure 5** shows exemplary synthetic pathways for deuterated d2-gaboxadol 4,4 and d2-gaboxadol 5,5.

[0120] **Figure 6** shows exemplary synthetic pathways for deuterated d4-gaboxadol 4,4,7,7, d4-gaboxadol 5,5,7,7, and d4-gaboxadol 4,4,5,5.

CLAIMS

What is claimed is:

1. A ring carbon deuterated gaboxadol compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof,

wherein R4, R4', R5, R5', R7 and R7' are independently H or D,

wherein D is present at five or more of R4, R4', R5, R5', R7 and R7', and

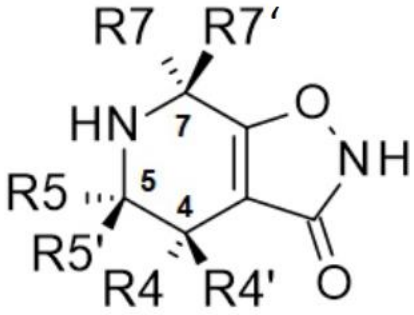
wherein the ring carbon deuterated gaboxadol compound is enriched with deuterium above the naturally occurring abundance of deuterium.

2. The compound of claim 1, wherein the percentage incorporation of deuterium is at least 1%.

3. The compound or salt of claim 1 or 2, wherein all of R4, R4', R5, and R5' are D, and at least one of R7 and R7' is D.

4. The compound or salt of claim 1 or 2 wherein all of R4, R4', R5, R5', R7 and R7' are D.

5. A composition comprising ring carbon deuterated gaboxadol compounds of Formula I



(I)

or a pharmaceutically acceptable salt thereof,
wherein R4, R4', R5, R5', R7 and R7' are independently H or D,
and wherein:
at least 50% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at all of R4, R4', R5, R5', R7 and R7'; or
at least 50% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at five positions selected from the group consisting of R4, R4', R5, R5', R7 and R7'.

6. The composition of claim 5, wherein at least 50% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at all of R4, R4', R5, R5', R7 and R7'.

7. The composition of claim 5, wherein at least 50% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at five positions selected from the group consisting of R4, R4', R5, R5', R7 and R7'.

8. The composition of claim 5, wherein at least 75% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at all of R4, R4', R5, R5', R7 and R7'.

9. The composition of claim 5, wherein in at least 85% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at all of R4, R4', R5, R5', R7 and R7'.

10. The composition of claim 5, wherein at least 90% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at all of R4, R4', R5, R5', R7 and R7'.

11. The composition of claim 5, wherein about 90% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at all of R4, R4', R5, R5', R7 and R7'.

12. The composition of claim 5, wherein at least 85% of the total compounds of Formula I or pharmaceutically acceptable salt thereof in the composition have D present at five positions selected from the group consisting of R4, R4', R5, R5', R7 and R7'.

13. A pharmaceutical composition comprising the compound or salt of any one of claims 1-4 or the composition of any one of claims 5-12, and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13, wherein the pharmaceutical composition is an oral dosage form.

15. The pharmaceutical composition of claim 14, wherein the pharmaceutical composition is a tablet.

16. The pharmaceutical composition of claim 14, wherein the oral dosage form is an orally disintegrating form.

17. The pharmaceutical composition of any one of claims 13-16, wherein the pharmaceutical composition comprises about 1 mg to about 300 mg of the compound or compounds of Formula I or salt thereof.

18. The pharmaceutical composition of any one of claims 13-16, wherein the pharmaceutical composition comprises about 50 mg to about 100 mg of the compound or compounds of Formula I or salt thereof.

19. The pharmaceutical composition of any one of claims 13-16, wherein the pharmaceutical composition comprises about 50 mg, about 75 mg, or about 100 mg of the compound or compounds of Formula I or salt thereof.

20. The pharmaceutical composition of any one of claims 13-16, wherein the pharmaceutical composition comprises about 25 mg to about 50 mg of the compound or compounds of Formula I or salt thereof.

21. The pharmaceutical composition of any one of claims 13-16, wherein the pharmaceutical composition comprises about 10 mg to about 30 mg of the compound or compounds of Formula I or salt thereof.

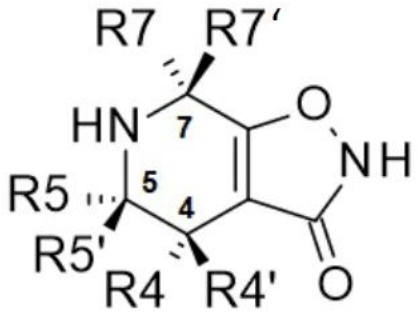
22. The pharmaceutical composition of any one of claims 13-21, further comprising at least one other compound selected from the group consisting of lithium, ketamine, AXS-05 (fixed combination of dextromethorphan and bupropion), SAGE-217, allopregnanolone, ganaxolone, alfadolone, alfaxolone, hydroxydione, minaxolone, pregnanolone, renanolone, 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, and [2-amino-4-(2,4,6-trimethylbenzylamino)-phenyl]-carbamic acid ethyl ester (AA29504).

23. The pharmaceutical composition of claim 22, wherein the at least one other compound is lithium.

24. The pharmaceutical composition of claim 22 or 23, wherein the pharmaceutical composition comprises 5 mg to 20 mg of the compound or compounds of Formula I or salt thereof.

25. A pharmaceutical composition, wherein the pharmaceutical composition comprises:

(a) a ring carbon deuterated gaboxadol compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof,

wherein R4, R4', R5, R5', R7 and R7' are independently H or D, and

wherein D is present at five or more of R4, R4', R5, R5', R7 and R7; and

(b) lithium or a pharmaceutically acceptable salt of lithium,

wherein the ring carbon deuterated compound is enriched with deuterium above the naturally occurring abundance of deuterium.

26. The pharmaceutical composition of claim 25, wherein all of R4, R4', R5, R5', R7 and R7' are D.

27. The pharmaceutical composition of claim 25 or 26, wherein the pharmaceutical composition is in a form of a single dosage unit having separate compartments for the lithium or lithium salt and ring carbon deuterated gaboxadol or ring carbon deuterated gaboxadol salt.

28. A method of making d6-gaboxadol, said method comprising:

(a) treating 3-hydroxypyridine-4-carboxylic acid with deuterium oxide under catalytic hydrogenation conditions to provide 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylic acid;

(b) treating 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylic acid from step (a) above with a methylating agent to provide methyl 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylate;

(c) treating methyl 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylate from step (b) above with hydroxylamine hydrochloride to provide 2,3,6-trideuterio-5-hydroxy-pyridine-4-carbohydroxamic acid;

(d) treating 2,3,6-trideuterio-5-hydroxy-pyridine-4-carbohydroxamic acid from step (c) above with an activating agent to provide 4,5,7-trideuterioisoxazolo[5,4-c]pyridin-3-one;

(e) treating 4,5,7-trideuterioisoxazolo[5,4-c]pyridin-3-one from step (d) above with a brominating agent to provide 6-benzyl-4,5,7-trideuterio-isoxazolo[5,4-c]pyridin-6-ium-3-ol bromide;

(f) treating 6-benzyl-4,5,7-trideuterio-isoxazolo[5,4-c]pyridin-6-ium-3-ol bromide from step (e) above with a reducing agent to provide 6-benzyl-4,4,5,5,7,7-hexadeuterio-isoxazolo[5,4-c]pyridin-3-ol; and

(g) deprotecting 6-benzyl-4,4,5,5,7,7-hexadeuterio-isoxazolo[5,4-c]pyridin-3-ol from step (f) above to remove the benzyl group to provide d6-gaboxadol.

29. The method of claim 28, wherein the method comprises:

(a) treating 3-hydroxypyridine-4-carboxylic acid with deuterium oxide in the presence of Pt/C and/or Pd/C and hydrogen gas at a temperature greater than 100 °C to provide 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylic acid;

(b) treating 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylic acid from step (a) above with methanol and sulfuric acid at reflux temperature to provide methyl 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylate;

(c) treating methyl 2,3,6-trideuterio-5-hydroxy-pyridine-4-carboxylate from step (b) above with hydroxylamine chloride and aqueous sodium hydroxide solution to provide 2,3,6-trideuterio-5-hydroxy-pyridine-4-carbohydroxamic acid;

(d) treating 2,3,6-trideuterio-5-hydroxy-pyridine-4-carbohydroxamic acid from step (c) above with thionyl chloride to provide 4,5,7-trideuterioisoxazolo[5,4-c]pyridin-3-one;

(e) treating 4,5,7-trideuterioisoxazolo[5,4-c]pyridin-3-one from step (d) above with benzyl bromide to provide 6-benzyl-4,5,7-trideuterio-isoxazolo[5,4-c]pyridin-6-ium-3-ol bromide;

(f) treating 6-benzyl-4,5,7-trideuterio-isoxazolo[5,4-c]pyridin-6-ium-3-ol bromide from step (e) above with deuterated sodium borohydride ($NaBD_4$) in a mixture of deuterated ethanol and/or deuterium oxide to provide 6-benzyl-4,4,5,5,7,7-hexadeuterio-isoxazolo[5,4-c]pyridin-3-ol; and

(g) treating 6-benzyl-4,4,5,5,7,7-hexadeuterio-isoxazolo[5,4-c]pyridin-3-ol from step (f) above with (i) methyl chloroformate in the presence of an inorganic base, followed by treatment with hydrobromic acid, or (ii) deuterated hydrobromic acid, to provide d6-gaboxadol.

30. Use of the compound of any one of claims 1-4 or the composition of any one of claims 5-12, in the manufacture of a medicament for treating a psychiatric disorder.

31. The use of claim 30, wherein the psychiatric disorder is bipolar disorder, depression, treatment-resistant depression, major depressive disorder, postpartum depression, or suicidality.

32. The use of claim 30, wherein the psychiatric disorder is depression.

33. The use of claim 30, wherein the psychiatric disorder is major depressive disorder.

34. The use of claim 30, wherein the psychiatric disorder is treatment resistant depression.

35. The use of any one of claims 30-34, wherein the medicament is to be administered once daily.

36. The use of any one of claims 30-35, wherein the medicament is to be administered at a dose of about 5 mg to about 10 mg, about 10 mg to about 30 mg, or about 25 mg to about 50 mg of the compound.

37. The use of any one of claims 30-34, wherein the medicament is to be administered at a daily dose of 50-100 mg of the compound.

38. The use of any one of claims 30-34, wherein the medicament is to be administered at a daily dose of 50, 75, or 100 mg of the compound.

39. The use of any one of claims 30-34, wherein 50-100 mg of the compound or salt is to be administered once daily for a first time period, followed by a washout period of at least one day during which the compound or salt is not to be administered, and wherein the compound or salt is to be administered daily for a second time period after the washout period.

40. Use of a combination of a ring carbon deuterated gaboxadol compound and lithium, or a pharmaceutically acceptable salt of the compound or lithium or both, in the manufacture of a medicament for treating a psychiatric disorder, wherein the compound is enriched with deuterium above the naturally occurring abundance of deuterium.

41. The use of claim 40, wherein the psychiatric disorder is bipolar disorder.42. The use of claim 40 or 41, wherein the ring carbon deuterated gaboxadol is to be administered at a dose of about 1 mg to about 20 mg.

43. The use of any one of claims 30-42, wherein the medicament is to be administered orally.