NEUROACTIVE STEROIDS, COMPOSITIONS, AND USES THEREOF

CLAIM OF PRIORITY

This application claims priority from U.S.S.N. 62/305,279 filed March 8, 2016, U.S.S.N. 62/355,174 filed June 27, 2016, U.S.S.N. 62/355,669 filed June 28, 2016, U.S.S.N. 62/360,758 filed July 11, 2016, and U.S.S.N. 62/360,762 filed July 11, 2016, all of which are incorporated herein by reference in their entireties.

BACKGROUND

Progesterone and its metabolites have been demonstrated to have profound effects on brain excitability (Backstrom, T. *et al., Acta Obstet. Gynecol. Scand. Suppl.* 130:19-24 (1985); Pfaff, D.W and McEwen, B. S., *Science* 219:808-814 (1983); Gyermek *et al., J Med Chem.* 11: 117 (1968); Lambert, J. *et al.*, *Trends Pharmacol. Sci.* 8:224-227 (1987)). The levels of progesterone and its metabolites vary with the phases of the menstrual cycle. It has been well documented that the levels of progesterone and its metabolites decrease prior to the onset of menses. The monthly recurrence of certain physical symptoms prior to the onset of menses has also been well documented. These symptoms, which have become associated with premenstrual syndrome (PMS), include stress, anxiety, and migraine headaches (Dalton, K., *Premenstrual Syndrome and Progesterone Therapy*, 2nd edition, Chicago Yearbook, Chicago (1984)). Subjects with PMS have a monthly recurrence of symptoms that are present in premenses and absent in postmenses.

A syndrome also related to low progesterone levels is postnatal depression (PND) or postpartum depression (PPD). Immediately after birth, progesterone levels decrease dramatically leading to the onset of PND. The symptoms of PND range from mild depression to psychosis requiring hospitalization. PND is also associated with severe anxiety and irritability. PND-associated depression is not amenable to treatment by classic antidepressants, and women experiencing PND show an increased incidence of PMS (Dalton, K., *Premenstrual Syndrome and Progesterone Therapy*, 2nd edition, Chicago Yearbook, Chicago (1984)).

Additionally, several lines of evidence suggest that cerebellar dysfunction through the cerebello-thalamocortical pathway play a key role in essential tremor (ET) (McAuley 2000; Pinto 2003; Elble 2009; Schnitzler 2009; Deuschl 2009). Activation studies with positron emission tomography (PET) indicate abnormally increased regional cerebral blood flow in the cerebellus both at rest and when tremor is provoked by unilateral arm extension (Boechker 1994, Wills 1996). Post-mortem analysis revealed a 35% reduction of $GABA_A$ receptors and a 22-31% reduction of $GABA_B$ receptors in the dentate nucleus of cerebella from ET patients (Paris-Robidas 2012).

There is increasing evidence to support the use of neuroactive steroids, *e.g.,* a neuroactive steroid as described herein, *e.g.,* progesterone and its metabolites; in the treatment and prevention of tremor (e.g., essential tremor), depression (e.g., postpartum depression, major depressive disorder), and anxiety disorder.

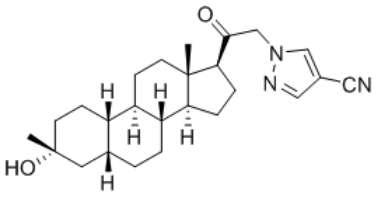
SUMMARY

The disclosure features, *inter alia*, a method, the method comprising administering a neuroactive steroid, *e.g.,* a neuroactive steroid as described herein, *e.g.,* pregnanolone, allopregnanolone, alphadalone, ganaxolone, alphaxolone, or Compound 9 as described below, or a pharmaceutical composition comprising a neuroactive steroid (e.g., brexanolone) to a subject, for example to treat a CNS-related disorder such as tremor, depression (e.g., postpartum depression, major depressive disorder), or anxiety disorder. In some embodiments, the neuroactive steroid is formulated for parenteral delivery (*e.g.*, intravenous delivery (IV)). The disclosure features methods of treating a subject having a CNS disorder, *e.g.,* tremor, *e.g.,* essential tremor; depression, *e.g.,* postpartum depression; and anxiety disorder, the methods comprising administering to the subject a composition described herein, *e.g.,* a neuroactive steroid, *e.g.,* pregnanolone, allopregnanolone, alphadalone, ganaxolone, or alphaxolone, and optionally a cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®. The disclosure also features, *inter alia*, compositions comprising a neuroactive steroid, *e.g.,* pregnanolone, allopregnanolone, alphadalone, ganaxolone, or alphaxolone; and optionally a cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* a β-cyclodextrin, *e.g.,* a sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL®.

In one aspect of the present disclosure, there is provided a use of a therapeutic agent in the manufacture of a medicament for treating a human subject, wherein:
a subject at risk of suffering from depression or an anxiety disorder is identified; and
a therapeutically effective amount of said therapeutic agent or a pharmaceutical composition comprising said therapeutic agent is to be administered to the subject.

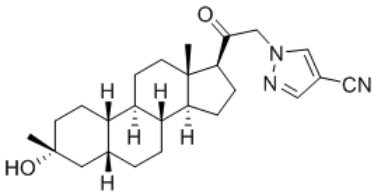
In another aspect of the present disclosure, there is provided Use of a neuroactive steroid or pharmaceutically acceptable salt or isotopologue thereof or a pharmaceutical composition comprising a neuroactive steroid or pharmaceutically acceptable salt or isotopologue thereof, in the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder.

In a further aspect of the present disclosure, there is provided Use of Compound 9, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof in the manufacture of a medicament for treating a disorder described herein, wherein a total daily dose of said medicament of about 10 mg to about 100 mg is to be orally administered to a subject in need thereof.



(Compound 9)

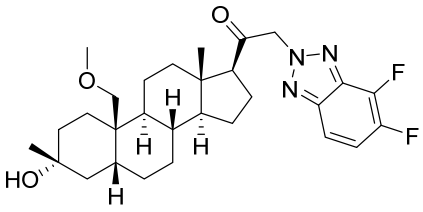
In another aspect of the present disclosure, there is provided Use of Compound 9 in the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder.



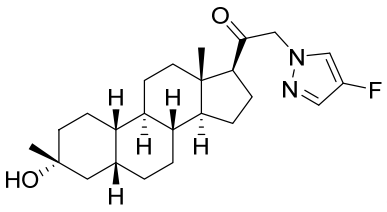
(Compound 9)

The present disclosure also provides a method for treating a human subject, the method comprising: identifying a subject at risk of suffering from depression (e.g., postpartum depression) or an anxiety disorder; and administering (e.g., orally, intraveneously) to the subject a therapeutically effective amount of a therapeutic agent (e.g., a neuroactive steroid as described herein (e.g., allopregnanolone)) or a pharmaceutical composition comprising a therapeutic agent (e.g., a pharmaceutical composition as described herein, e.g., brexanolone). In some embodiments, the therapeutic agent is administered to the subject within 3 days, 2 days, 1 day, or 24 hours of delivery of a baby (e.g., within 12 hours, within 6 hours, within 3 hours, within 2 hours, within 1 hour, within 30 minutes).

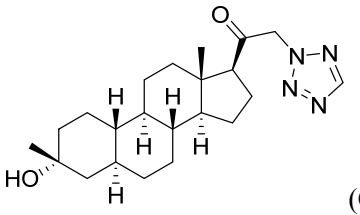
In some embodiments, the subject is identified to be at risk through a screening method (e.g., Edinburgh Postnatal Depression Scale (EPDS), e.g., a score of 10 or more on the EPDS, a score of 13 or more on the EPDS). In some embodiments, the subject is identified to be at risk through screening instruments such as Patient Health Questionnaire (PHQ) in various forms or the Hospital Anxiety and Depression Scales or Geriatric Depression Scale.



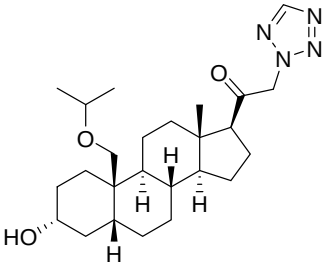
(Compound 15),



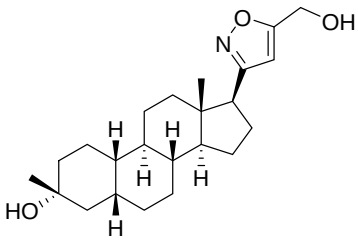
(Compound 16),



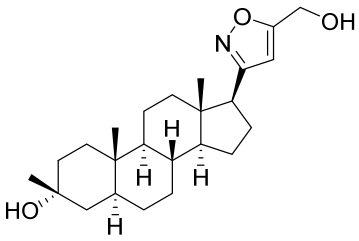
(Compound 17),



(Compound 18),



(Compound 19),



(Compound 20),

or a pharmaceutically acceptable salt or isotopologue thereof.

In some embodiments, the pharmaceutical composition is brexanolone. In some embodiments, the therapeutic agent is Compound 9 or a pharmaceutically acceptable salt or isotopologue thereof.

In some embodiments, when the therapeutic agent is allopregnanolone, then the therapeutic agent or pharmaceutical composition comprising the therapeutic agent (e.g., brexanolone) is administered parenterally, wherein administering occurs through an intermittent intravenous infusion or continuous intravenous infusion. In some embodiments, when the therapeutic agent is Compound 9, then the therapeutic agent or pharmaceutical composition comprising the therapeutic agent is administered orally. In some embodiments, the neuroactive steroid or pharmaceutical composition comprising the neuroactive steroid is administered chronically. In some embodiments, the neuroactive steroid or pharmaceutical composition comprising the neuroactive steroid is administered acutely.

The present disclosure also provides a method for treating a human subject suffering from depression (e.g., postpartum depression or major depressive disorder) or an anxiety disorder, the method comprising administering (e.g., orally, intraveneously) to the subject a therapeutically effective amount of a neuroactive steroid (e.g., allopregnanolone) or pharmaceutically acceptable salt or isotopologue thereof or a pharmaceutical composition comprising a neuroactive steroid or pharmaceutically acceptable salt or isotopologue thereof (e.g., brexanolone).

emergency C-sections, pre-eclampsia, hospitalization during pregnancy, concern about fetal distress and admission of the baby to special care (NICU), the baby was in the NICU). In some embodiments, the subject has had emotionally painful or stressful experiences around pregnancy, childbirth, or early parenting (e.g., the subject was treated for infertility, had a previous miscarriage or other pregnancy loss, delivery of muliples, special needs, colic or difficult temperament baby, had difficulty feeding). In some embodiments, the subject has had a history of domestic violence, sexual or other abuse (e.g., abused as a child or as an adult). In some embodiments, the subject has had a traumatic childhood (e.g., loss of a parent, troubling relationship with parent). In some embodiments, the subject has stress (e.g., loss of someone close, job loss, financial hardship, divorce, strain in a relationship, house move). In some embodiments, the subject has lack of social support. In some embodiments, the subject has a perfectionist or controlling personality. In some embodiments, the subject is a female. In some embodiments, the female is not breast feeding. In some embodiments, the subject is an adult. In some embodiments, the subject is from 18 to 45 years of age. In some embodiments, the subject is suffering from (*e.g.,* has been diagnosed with) postpartum depression (*e.g.,* severe postpartum depression). In some embodiments, the subject has experienced a Major Depressive Episode in the postpartum period. In some embodiments, the period begins within the first 4 weeks following delivery of a baby.

The present disclosure further provides a method of treating a human subject suffering from tremor, the method comprising administering a therapeutically effective amount of a neuroactive steroid. In some embodiments, the method does not result in sedation. In some embodiments, the tremor is essential tremor.

In some embodiments, the administering is performed parenterally. In some embodiments, the administering is performed intravenously.

In some embodiments, the administering is performed orally.

In some embodiments, the administering comprises administering one or more cycles of treatment, a cycle of treatment comprising: administering a first dose of the neuroactive steroid; administering a second dose of the neuroactive steroid; and administering a third dose of the neuroactive steroid, said neuroactive steroid doses being sufficient to treat said subject.

In some embodiments, the first dose is 20 to 40 μg/kg/hr (*e.g.,* about 30 μg/kg/hr, 29 μg/kg/hr). In some embodiments, the second dose is 45 to 65 μg/kg/hr (*e.g.,* about 60 μg/kg/hr, 58 μg/kg/hr). In some embodiments, the third dose is 80 to 100 μg/kg/hr (*e.g.,* about 90 μg/kg/hr, 86 μg/kg/hr). In some embodiments, each of the first, second, and third doses are 2 to 6 hours (*e.g.,* 4 hours) in duration. In

In some embodiments, the subject has been diagnosed with essential tremor. In some embodiments, the subject has suffered from tremor for at least 2 years.

The present disclosure also provides a method of treating a subject suffering from tremor (*e.g.,* essential tremor), comprising: administering a first dose, wherein administration of said first dose; and results in a plasma level of neuroactive steroid of 50 to 300 nM neuroactive steroid; a rest period comprising at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days; and administering a second dose, wherein administration of said second dose; and results in a plasma level of neuroactive steroid of 50 to 300 nM neuroactive steroid; wherein, collectively, the administrations are provided in sufficient amount to treat said subject. In some embodiments, the method does not result in sedation.

The present disclosure further provides a method of treating a subject suffering from tremor (*e.g.,* essential tremor), comprising: administering a first dose, wherein administration of said first dose lasts for at least 1 day; and results in a plasma level of neuroactive steroid of 100 to 200 nM neuroactive steroid; a rest period comprising at least 5, 6, or 7 days; and administering a second dose, wherein administration of said second dose lasts for at least 1 day; and results in a plasma level of neuroactive steroid of 100 to 200 nM neuroactive steroid; wherein, collectively, the administrations are provided in sufficient amount to treat said subject. In some embodiments, the method does not result in sedation.

The present disclosure also provides a method of treating a subject suffering from tremor (*e.g.,* essential tremor), comprising: administering a first dose, wherein administration of said first dose lasts for 1 day; and results in a plasma level of neuroactive steroid of 150 nM neuroactive steroid; a rest period comprising 7 days; and administering a second dose, wherein administration of said second dose lasts for 1 day; and results in a plasma level of neuroactive steroid of 150 nM neuroactive steroid; wherein, collectively, the administrations are provided in sufficient amount to treat said subject. In some embodiments, the method does not result in sedation.

In some embodiments, the administration of the second dose begins no longer than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 days after the beginning or end of the administration of the first dose. In some embodiments, the second dose begins 1 to 14, 3 to 12, 5 to 10, or 7 days after the beginning or end of the administration of the first dose. In some embodiments, the second dose begins no more than 14, 12, 10, 9, 8, 7, 6, 5, 3, 2, or 1 day after the end of administration of the first dose. In some embodiments, the first dose and the initiation of the second dose are performed with the same delivery device, *e.g.,* with the same cannula or reservoir. In some embodiments, the plasma concentration of said third dose is measured at a preselected time, *e.g.,* at 10, 15, 20, 30, 45, or 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, or 24 hours, or 2, 3, or 4 days after the initiation of said third dose. In some embodiments, said third dose results in a plasma

concentration of 150 nM, *e.g.,* as measured at a preselected time, *e.g.,* at 10, 15, 20, 30, 45, or 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, or 24 hours, or 2, 3, or 4 days after the initiation of said third dose.

The present disclosure also provides a method of treating a subject suffering from tremor (e.g., essential tremor) comprising the steps of: a) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone or Compound 9) in reducing tremor (e.g., symptoms of tremor) in a subject treated with the neuroactive steroid (e.g., allopregnanolone or Compound 9); and b) administering to the subject a therapeutic agent (e.g., neuroactive steroid) if the information indicates that tremor (e.g., symptoms of tremor) is reduced in the subject as compared to the subject before having received the neuroactive steroid (e.g., allopregnanolone or Compound 9), thereby treating the subject.

The present disclosure further provides a method of selecting a therapeutic agent (e.g., a neuroactive steroid) for treating tremor (e.g., essential tremor) in a human subject treated with a neuroactive steroid (e.g., allopregnanolone or Compound 9) comprising the steps of: a) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone or Compound 9) in reducing tremor (e.g., symptoms of tremor) in a subject; and b) selecting the therapeutic agent (e.g., neuroactive steroid) if the information indicates that tremor (e.g., symptoms of the depression or anxiety disorder) is reduced in the subject as compared to the subject before having received the neuroactive steroid (e.g., allopregnanolone or Compound 9).

The present disclosure also providesa method of evaluating (e.g., diagnosing, prognosing, and determining a course of treatment in) a subject suffering from tremor (e.g., essential tremor), comprising the steps of:
a) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) in reducing tremor (e.g., symptoms of tremor) in a subject treated with the neuroactive steroid (e.g., allopregnanolone); and b) determining if tremor (e.g., symptoms of tremor) is reduced in the subject as compared to the subject before receiving the neuroactive steroid (e.g., allopregnanolone), thereby evaluating the subject.

In some embodiments, the information is received, e.g., about 1, 2, 3, 4, 5, or 6 days; about 1, 2, or 3 weeks; about 1, 2, or 3 months after administration of the neuroactive steroid (e.g., allopregnanolone).

In some embodiments, the subject has been administered the neuroactive steroid less than about 3 months (e.g., less than about 2 or 1 month; 3, 2, or 1 weeks; 6, 5, 4, 3, 2, or 1 days) prior to receiving the information. In some embodiments, the subject has been administered the neuroactive steroid (e.g., allopregnanolone) by intravenous infusion.

In some embodiments, the therapeutic agent is administered by oral administration. In some embodiments, the therapeutic agent is administered as a solid composition (e.g., a solid dosage form).

The present disclosure further provides a method of evaluating (e.g., diagnosing, prognosing, or determining a course of treatment in) a subject suffering from tremor (e.g., essential tremor), comprising the steps of: a) administering to the subject a therapeutic agent (e.g., neuroactive steroid); and b) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) in reducing tremor (e.g., symptoms of tremor) in a subject treated with the neuroactive steroid (e.g., allopregnanolone), thereby evaluating the subject. In some embodiments, the information is acquired by imaging the subject or a sample from the subject. In some embodiments, the information is acquired by fMRI. In some embodiments, the information is acquired by SPECT.

The present disclosure also provides a method for treating a human subject suffering from depression (*e.g.,* postpartum depression) or an anxiety disorder, the method comprising: administering a first infusion of a neuroactive steroid, wherein said first/step-up infusion is administered for 8-16 hours (*e.g.,* 12 hours);administering a second/maintenance infusion of a neuroactive steroid, wherein said second/maintenance infusion is administered for 24-48 hours (*e.g.,* 36 hours); and administering a third infusion of a neuroactive steroid, wherein said third/downward taper infusion is administered for 8-16 hours (*e.g.,* 12 hours); said neuroactive steroid doses being sufficient to treat said subject.

In some embodiments, the subject is identified to be at risk through a screening method (e.g., Edinburgh Postnatal Depression Scale (EPDS), e.g., a score of 10 or more on the EPDS, a score of 13 or more on the EPDS). In some embodiments, the subject is identified to be at risk through screening instruments such as Patient Health Questionnaire (PHQ) in various forms or the Hospital Anxiety and Depression Scales or Geriatric Depression Scale.

In some embodiments, the subject has given birth. In some embodiments, the subject has given birth within 3, 2, 1 days; 24, 20, 16, 12, 8, 6, 4, 3, 2, 1 hours; 60, 45, 30, 15, 10, 5 minutes. In some embodiments, the subject is due to give birth. In some embodiments, the subject is due to give birth in 9, 8, 7, 6, 5, 4, 3, 2, 1 months; 4, 3, 2, 1 weeks; 7, 6, 5, 4, 3, 2, 1 days.

In some embodiments, the subject has an attribute, characteristic, or exposure (that increases the likelihood of developing a disorder as described herein, e.g., neuroactive steroid deficiency). In some embodiments, the subject has a chronic illness (e.g., cancer or cardiovascular disease), other mental health disorders (including substance misuse), or a family history of psychiatric disorders. In some embodiments, the subject is disabled or has poor health status due to medical illness, complicated grief, chronic sleep disturbance, loneliness, or history of depression. In some embodiments, the subject has poor self-esteem, child-care stress, prenatal anxiety, life stress, decreased social support,

single/unpartnered relationship status, history of depression, difficult infant temperament, previous postpartum depression, lower socioeconomic status, or unintended pregnancy.

In some embodiments, the subject has hyperemesis gravidarum (e.g., severe form of morning sickness, e.g., preventing adequate intake of food and fluids). In some embodiments, the subject has had a complication in pregnancy (e.g., emergency C-sections, pre-eclampsia, hospitalization during pregnancy, concern about fetal distress and admission of the baby to special care (NICU), the baby was in the NICU). In some embodiments, the subject has had emotionally painful or stressful experiences around pregnancy, childbirth, or early parenting (e.g., the subject was treated for infertility, had a previous miscarriage or other pregnancy loss, delivery of muliples, special needs, colic or difficult temperament baby, had difficulty feeding). In some embodiments, the subject has had a history of domestic violence, sexual or other abuse (e.g., abused as a child or as an adult). In some embodiments, the subject has had a traumatic childhood (e.g., loss of a parent, troubling relationship with parent). In some embodiments, the subject has stress (e.g., loss of someone close, job loss, financial hardship, divorce, strain in a relationship, house move). In some embodiments, the subject has lack of social support. In some embodiments, the subject has a perfectionist or controlling personality.

The present disclosure further provides a method for treating a human subject suffering from depression (*e.g.,* postpartum depression or major depressive disorder) or an anxiety disorder, the method comprising: administering a first infusion of a neuroactive steroid, said first/step-up infusion comprising administering a continuously increasing amount of neuroactive steroid at an amount of neuroactive steroid/unit time of 5-100 μg/kg/hour, 10-80 μg/kg/hour, 15-70 μg/kg/hour, or 30 μg/kg/hour; administering a second/maintenance infusion of a neuroactive steroid, said second/maintenance infusion comprising administering an amount of neuroactive steroid/unit time of 50-100 μg/kg/hour, 70-100 μg/kg/hour, 86 μg/kg/hour, or 60 μg/kg/hour; and administering a third infusion of a neuroactive steroid, said third/downward taper infusion comprising administering a continuously decreasing amount of neuroactive steroid at an amount of neuroactive steroid/unit time of 5-100 μg/kg/hour, 10-80 μg/kg/hour, 15-70 μg/kg/hour, or 90 μg/kg/hour; said neuroactive steroid doses being sufficient to treat said subject.

In some embodiments, the method provides therapeutic effect (e.g., as measured by reduction in Hamilton Depression Score (HAM-D)) within 4, 3, 2, or 1 days; or 24, 20, 16, 12, 10, or 8 hours or less. In some embodiments, the therapeutic effect is a decrease from baseline in HAM-D score at the end of a treatment period (e.g., 12, 24, or 48 hours after administration; or 24, 48, 60, 72, or 96 hours or more).

In some embodiments, the subject has hyperemesis gravidarum (e.g., severe form of morning sickness, e.g., preventing adequate intake of food and fluids). In some embodiments, the subject has had a complication in pregnancy (e.g., emergency C-sections, pre-eclampsia, hospitalization during pregnancy, concern about fetal distress and admission of the baby to special care (NICU), the baby was in the NICU). In some embodiments, the subject has had emotionally painful or stressful experiences around pregnancy, childbirth, or early parenting (e.g., the subject was treated for infertility, had a previous miscarriage or other pregnancy loss, delivery of muliples, special needs, colic or difficult temperament baby, had difficulty feeding). In some embodiments, the subject has had a history of domestic violence, sexual or other abuse (e.g., abused as a child or as an adult). In some embodiments, the subject has had a traumatic childhood (e.g., loss of a parent, troubling relationship with parent). In some embodiments, the subject has stress (e.g., loss of someone close, job loss, financial hardship, divorce, strain in a relationship, house move). In some embodiments, the subject has lack of social support. In some embodiments, the subject has a perfectionist or controlling personality.

The present disclosure also provides a method of treating a subject suffering from depression or an anxiety disorder comprising the steps of: a) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone or Compound 9) in reducing the depression or anxiety disorder (e.g., symptoms of the depression or anxiety disorder) in a subject treated with the neuroactive steroid (e.g., allopregnanolone or Compound 9); and b) administering to the subject a therapeutic agent (e.g., a neuroactive steroid) if the information indicates that the depression or anxiety disorder (e.g., symptoms of the depression or anxiety disorder) is reduced in the subject as compared to the subject before having received the neuroactive steroid (e.g., allopregnanolone or Compound 9), thereby treating the subject. In some embodiments, the depression is major depressive disorder. In some embodiments, the depression is postpartum depression.

The present disclosure further provides a method of selecting a therapeutic agent (e.g., a neuroactive steroid) for treating depression or an anxiety disorder in a human subject treated with a neuroactive steroid (e.g., allopregnanolone or Compound 9) comprising the steps of: a) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone or Compound 9) in reducing the depression or anxiety disorder (e.g., symptoms of the depression or anxiety disorder) in a subject; and b) selecting the therapeutic agent (e.g., neuroactive steroid) if the information indicates that the depression or anxiety disorder (e.g., symptoms of the depression or anxiety disorder) is reduced in the subject as compared to the subject before having received the neuroactive steroid (e.g., allopregnanolone or Compound 9). In some embodiments, the depression is major depressive disorder. In some embodiments, the depression is postpartum depression.

The present disclosure also providesa method of evaluating (e.g., diagnosing, prognosing, and determining a course of treatment in) a subject suffering from depression or anxiety disorder, comprising the steps of:

a) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone or Compound 9) in reducing depression or anxiety disorder (e.g., symptoms of the depression or anxiety disorder) in a subject treated with the neuroactive steroid (e.g., allopregnanolone or Compound 9); and b) determining if the depression or anxiety disorder (e.g., symptoms of the depression or anxiety disorder) is reduced in the subject as compared to the subject before receiving the neuroactive steroid (e.g., allopregnanolone), thereby evaluating the subject. In some embodiments, the information is received, e.g., about 1, 2, 3, 4, 5, or 6 days; about 1, 2, or 3 weeks; about 1, 2, or 3 months after administration of the neuroactive steroid (e.g., allopregnanolone). In some embodiments, the subject has been administered the neuroactive steroid less than about 3 months (e.g., less than about 2 or 1 month; 3, 2, or 1 weeks; 6, 5, 4, 3, 2, or 1 days) prior to receiving the information. In some embodiments, the subject has been administered the neuroactive steroid (e.g., allopregnanolone) by intravenous infusion. In some embodiments, the therapeutic agent is administered by oral administration. In some embodiments, the therapeutic agent is administered as a solid composition (e.g., a solid dosage form).

The present disclosure further providesa method of evaluating (e.g., diagnosing, prognosing, or determining a course of treatment in) a subject suffering from depression or anxiety disorder, comprising the steps of:

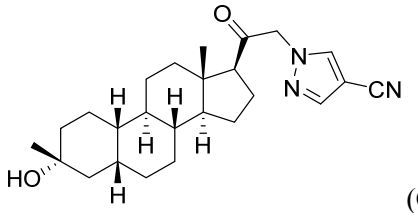
a) administering to the subject a therapeutic agent (e.g., neuroactive steroid or Compound 9); and b) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone or Compound 9) in reducing the depression or anxiety disorder (e.g., symptoms of the depression or anxiety disorder) in a subject treated with the neuroactive steroid (e.g., allopregnanolone or Compound 9), thereby evaluating the subject. In some embodiments, the information is acquired by imaging the subject or a sample from the subject. In some embodiments, the information is acquired by fMRI. In some embodiments, the information is acquired by SPECT.

The present disclosure also providesa method of treating a subject suffering from a neuroendocrine disease (or neuroendocrine dysfunction), comprising: intravenously administering to the subject a therapeutically effective amount of a neuroactive steroid (e.g., allopregnanolone), wherein administering occurs by continuous intravenous infusion or intermittent intravenous infusion. In some embodiments, the concentrations of allopregnanolone in plasma is greater than that in a normal subject. In some embodiments, the concentrations of allopregnanolone in plasma is 10 nM in plasma or less.

The present disclosure further providesa method of treating a symptom of a neuroendocrine diseases (or neuroendocrine dysfunction), comprising: intravenously administering to the subject a therapeutically effective amount of a neuroactive steroid (e.g., allopregnanolone), wherein administering occurs by continuous intravenous infusion. In some embodiments, the symptom is reduced at a magnitude or rate different from that observed in a subject without having received treatment.

The present disclosure also providesa method of increasing allopregnanolone levels in a subject (e.g., a subject with low levels of allopregnanolone as compared with a subject with normal levels of allopregnanolone), comprising: intravenously administering to the subject a therapeutically effective amount of a neuroactive steroid (e.g., allopregnanolone), wherein administering occurs by continuous intravenous infusion or intermittent infusion.

The present disclosure further providesmethods for treating a disease or disorder described herein, comprising administering to a subject a therapeutically effective amount of Compound 9



(Compound 9)

or pharmaceutically acceptable salt or isotopologue thereof.

The present disclosure also providesa method for treating or preventing a disorder described herein, comprising orally administering a total daily dose of Compound 9, or pharmaceutically acceptable salt or isotopologue thereof, or pharmaceutical composition thereof of about 10 mg to about 100 mg to a subject in need thereof.

In some embodiments, Compound 9, or a pharmaceutically acceptable salt or isotopologue thereof, or pharmaceutical composition thereof is administered chronically. In some embodiments, Compound 9, or pharmaceutically acceptable salt or isotopologue thereof, or pharmaceutical composition thereof is administered acutely.

In some embodiments, the disease or disorder is a GABA-related disease or disorder. In some embodiments, the GABA receptor is modulated (e.g., as determined by assessment of electrical activity in the brain using an electroencephalogram (EEG)). In some embodiments, the GABA receptor is modulated (e.g., as determined by assessment of electrical activity in the brain by beta-band EEG).

In some embodiments, the subject is administered about 10 mg to about 80 mg (e.g., about 10 mg to about 60 mg) of the compound. In some embodiments, the subject is administered about 10 mg to about 50 mg (e.g., about 35 mg) of the compound. In some embodiments, the subject is administered less

embodiments, the subject does not experience impact on cognition e.g., as measured by testing of psychomotor function, attention, visual learning, or executive function.

In some embodiments, the method further comprises administering an additional therapeutic agent.

The present disclosure further provides a method for treating a human subject, the method comprising: identifying a subject at risk of suffering from depression (e.g., postpartum depression) or an anxiety disorder; and administering (e.g., orally, intraveneously) to the subject a therapeutically effective amount of Compound 9.

In some embodiments, the therapeutic agent is administered to the subject within 3 days, 2 days, 1 day, 24 hours of delivery of a baby (e.g., within 12 hours, within 6 hours, within 3 hours, within 2 hours, within 1 hour, within 30 minutes). In some embodiments, Compound 9 or a composition comprising Compound 9 is administered orally.

In some embodiments, the subject is identified to be at risk through a screening method (e.g., Edinburgh Postnatal Depression Scale (EPDS), e.g., a score of 10 or more on the EPDS, a score of 13 or more on the EPDS). In some embodiments, the subject has given birth (e.g., the subject has given birth within 3, 2, 1 days; 24, 20, 16, 12, 8, 6, 4, 3, 2, 1 hours; 60, 45, 30, 15, 10, 5 minutes). In some embodiments, the subject is due to give birth. In some embodiments, the subject is due to give birth in 9, 8, 7, 6, 5, 4, 3, 2, 1 months; 4, 3, 2, 1 weeks; 7, 6, 5, 4, 3, 2, 1 days. In some embodiments, the subject has an attribute, characteristic, or exposure (that increases the likelihood of developing a disorder as described herein, e.g., neuroactive steroid deficiency). In some embodiments, the subject has hyperemesis gravidarum (e.g., severe form of morning sickness, e.g., preventing adequate intake of food and fluids). In some embodiments, the subject has had a complication in pregnancy (e.g., emergency C-sections, pre-eclampsia, hospitalization during pregnancy, concern about fetal distress and admission of the baby to special care (NICU), the baby was in the NICU). In some embodiments, the subject has had emotionally painful or stressful experiences around pregnancy, childbirth, or early parenting (e.g., the subject was treated for infertility, had a previous miscarriage or other pregnancy loss, delivery of muliples, special needs, colic or difficult temperament baby, had difficulty feeding). In some embodiments, the subject has had a history of domestic violence, sexual or other abuse (e.g., abused as a child or as an adult). In some embodiments, the subject has had a traumatic childhood (e.g., loss of a parent, troubling relationship with parent). In some embodiments, the subject has stress (e.g., loss of someone close, job loss, financial hardship, divorce, strain in a relationship, house move). In some embodiments, the subject has lack of social support. In some embodiments, the subject has a

perfectionist or controlling personality. In some embodiments, the therapeutic agent is a Selective Serotonin Reuptake Inhibitor (SSRI).

The present disclosure also providesa method for treating a human subject suffering from major depressive disorder (e.g., postpartum depression) or an anxiety disorder, the method comprising administering (e.g., orally, intraveneously) to the subject a therapeutically effective amount of Compound 9.

The present disclosure further providesa method for treating a human subject suffering from depression (e.g., postpartum depression) or an anxiety disorder, the method comprising administering (e.g., orally, intraveneously) to the subject a therapeutically effective amount of Compound 9.

In some embodiments, the depression is clinical depression (e.g., severe depression), postnatal or postpartum depression, atypical depression, melancholic depression, Psychotic Major Depression (PMD), catatonic depression, Seasonal Affective Disorder (SAD), dysthymia, double depression, Depressive Personality Disorder (DPD), Recurrent Brief Depression (RBD), minor depressive disorder, bipolar disorder or manic depressive disorder, post-traumatic stress disorders, depression caused by chronic medical conditions, treatment-resistant depression, refractory depression, suicidality, suicidal ideation, or suicidal behavior. In some embodiments, the depression is severe depression. In some embodiments, the depression is postpartum depression. In some embodiments, the depression is major depressive disorder.

In some embodiments, the method provides acute treatment of the depression (e.g., within 72 hours, 48 hours, 24 hours, 12 hours, or less). In some embodiments, the method provides maintenance treatment or preventative treatment. In some embodiments, the method provides acute treatment of the depression or anxiety disorder (e.g., provides relief from a symptom in less than 1 week (e.g., within 6 days, 5 days, 4 days, 3 days, 2 days, 1 day, or 12 hours). In some embodiments, the method provides rapid onset of efficacy (e.g., rapid reduction in a symptom of depression or anxiety disorder; rapidly affective to reduce a symptom of depression or anxiety disorder, e.g., a subject experiences relief from a symptom of depression or anxiety disorder described herein within 1 week (e.g., within 6 days, 5 days, 4 days, 3 days, 2 days, 1 day, or 12 hours)). In some embodiments, the therapeutic effect is sustained (e.g., effectively treats a symptom of depression or anxiety disorder and the efficacy is maintained for at least 1 day (e.g., at least 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, or more). In some embodiments, the efficacy is maintained after a single course of treatment (e.g., single dose, multiple doses, or cycle of treatment) of Compound 9.

CLAIMS

1. Use of a therapeutic agent in the manufacture of a medicament for treating a human subject, wherein:

a subject at risk of suffering from depression or an anxiety disorder is identified; and

a therapeutically effective amount of said therapeutic agent or a pharmaceutical composition comprising said therapeutic agent is to be administered to the subject.

2. The use of claim 1, wherein the medicament is to be administered to the subject within 3 days, 2 days, 1 day, 24 hours of delivery of a baby.

3. The use of claim 1, wherein the subject is identified to be at risk through a screening method.

4. The use of claim 1, wherein the subject has given birth.

5. The use of claim 1, wherein the subject is due to give birth.

6. The use of claim 5, wherein the subject is due to give birth in 9, 8, 7, 6, 5, 4, 3, 2, or 1 months; 4, 3, 2, or 1 weeks; or 7, 6, 5, 4, 3, 2, or 1 days.

7. The use of claim 1, wherein the subject has an attribute, characteristic, or exposure that increases the likelihood of developing a disorder .

8. The use of claim 7, wherein the subject has hyperemesis gravidarum.

9. The use of claim 7, wherein the subject has had a complication in pregnancy.

10. The use of claim 7, wherein the subject has had emotionally painful or stressful experiences around pregnancy, childbirth, or early parenting.

11. The use of claim 7, wherein the subject has had a history of domestic violence, sexual or other abuse.

12. The use of claim 7, wherein the subject has had a traumatic childhood.

13. The use of claim 7, wherein the subject has stress.

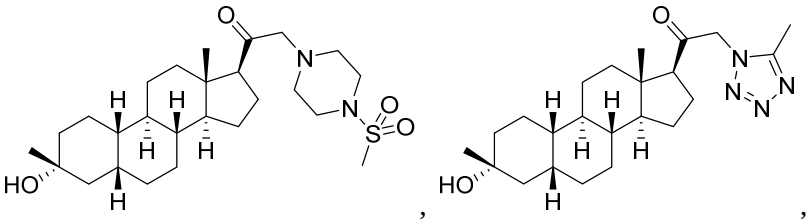
14. The use of claim 7, wherein the subject has lack of social support.

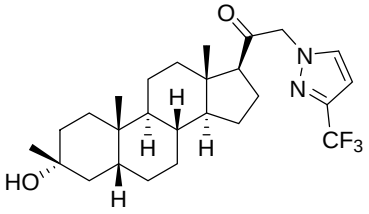
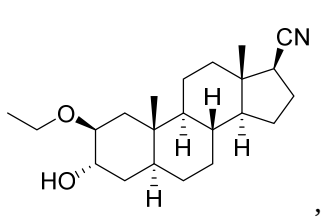
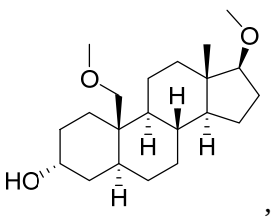
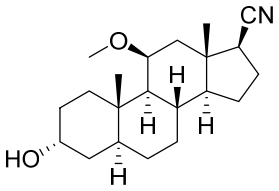
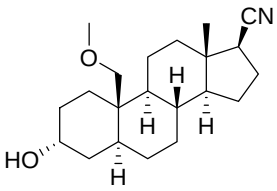
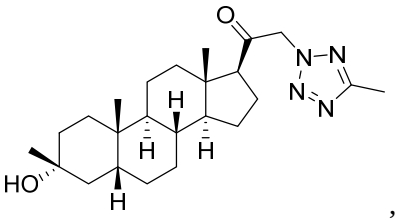
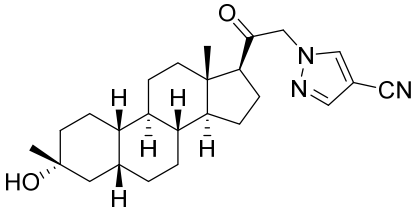
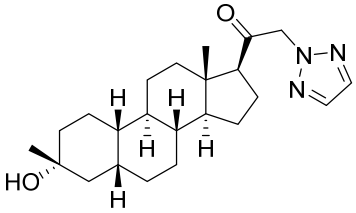
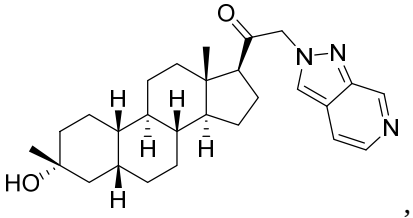
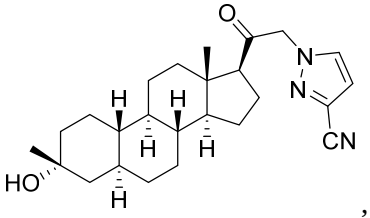
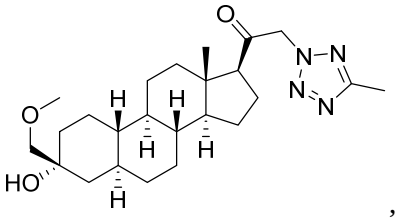
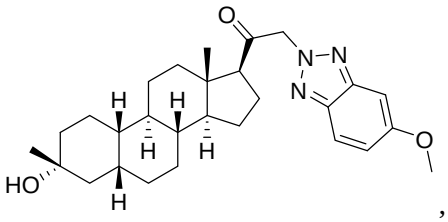
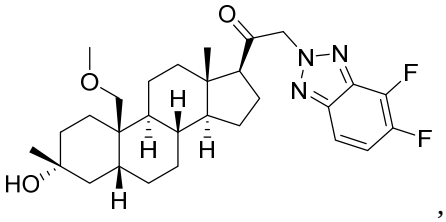
15. The use of claim 7, wherein the subject has a perfectionist or controlling personality.

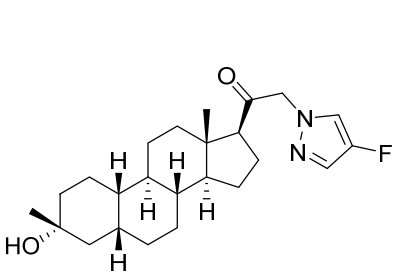
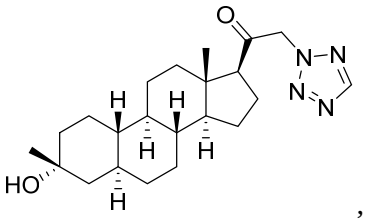
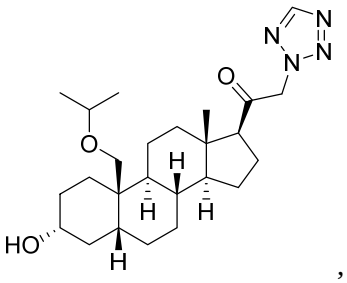
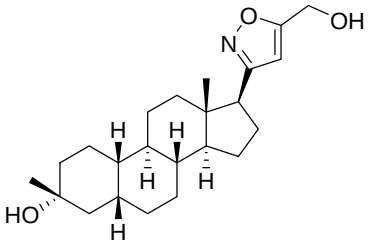
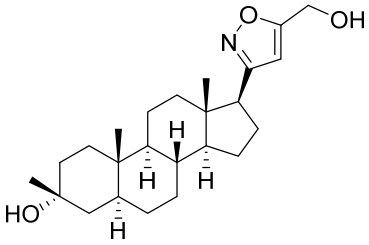
16. The use of claim 1, wherein the therapeutic agent is a neuroactive steroid selected from pregnanolone, ganaxolone, alphadalone, alphaxalone, and allopregnanolone.

17. The use of claim 1, wherein the pharmaceutical composition is brexanolone.

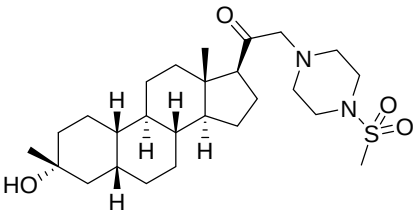
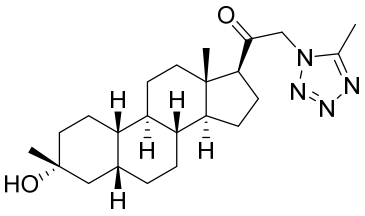
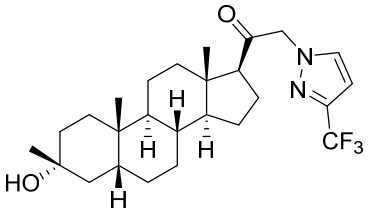
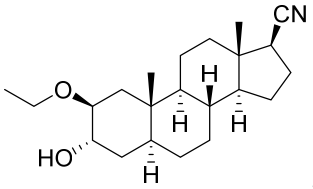
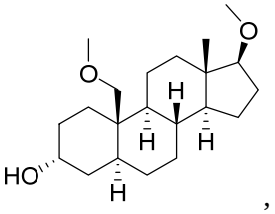
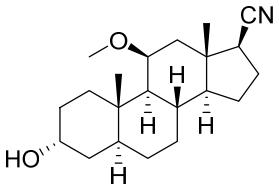
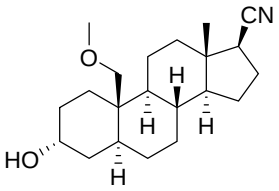
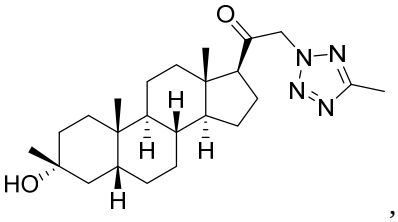
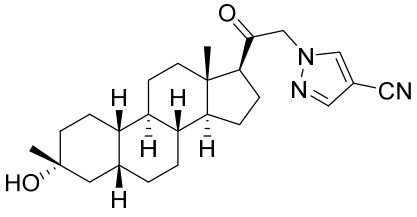
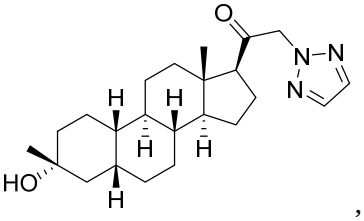
18. The use of claim 1, wherein the therapeutic agent is:

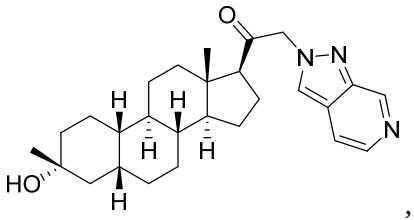
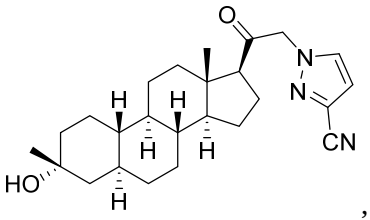
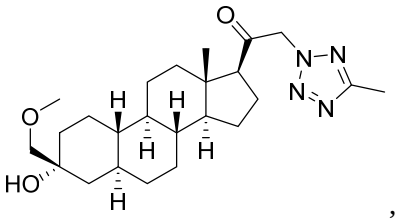
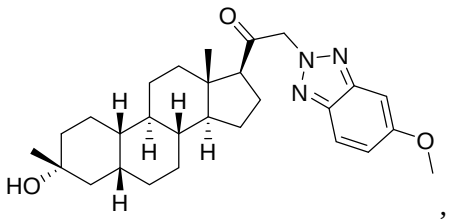
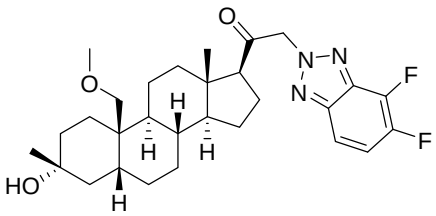
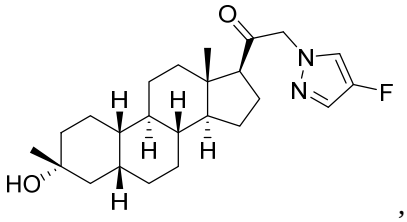
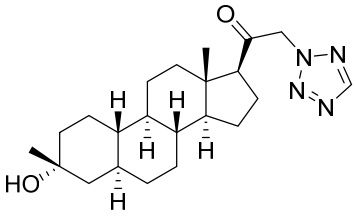
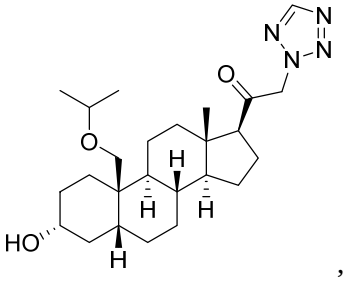
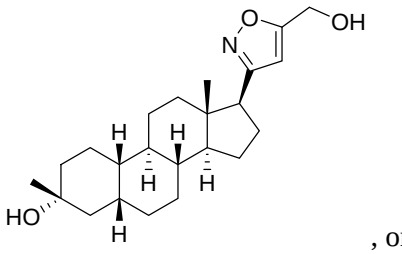
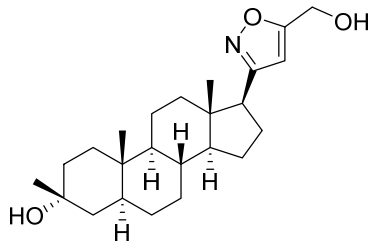

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19. The use of claim 1, wherein the therapeutic agent is a pharmaceutically acceptable salt of


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20. Use of a neuroactive steroid or pharmaceutically acceptable salt or isotopologue thereof or a pharmaceutical composition comprising a neuroactive steroid or pharmaceutically acceptable salt or isotopologue thereof, in the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder.

21. The use of claim 20, wherein the depression is clinical depression, postnatal or postpartum depression, atypical depression, melancholic depression, Psychotic Major Depression (PMD), catatonic depression, Seasonal Affective Disorder (SAD), dysthymia, double depression, Depressive Personality Disorder (DPD), Recurrent Brief Depression (RBD), minor depressive disorder, bipolar disorder or manic depressive disorder, post-traumatic stress disorders, depression caused by chronic medical conditions, treatment-resistant depression, refractory depression, suicidality, suicidal ideation, or suicidal behavior.

22. The use of claim 20, wherein the depression is severe depression.

23. The use of claim 20, wherein the depression is postpartum depression.

24. The use of claim 20, wherein the depression is major depressive disorder.

25. The use of claim 20, wherein the use provides acute treatment of the depression.

26. The use of claim 20, wherein the use provides maintenance treatment or preventative treatment.

27. The use of claim 20, wherein the use provides acute treatment of the depression or anxiety disorder.

28. The use of claim 20, wherein the use provides a rapid onset of efficacy.

29. The use of claim 20, wherein a therapeutic effect is sustained.

30. The use of claim 20, wherein the efficacy is maintained after a single course of treatment.

31. The use of claim 20, wherein the therapeutic effect does not cause an adverse event.

32. The use of claim 20, wherein the use includes a course of treatment with multiple dosages or cycles of treatment.

33. The use of claim 20, wherein a first and second dose or cycle of treatment include the same compound.

34. The use of claim 20, wherein the first dose or cycle of treatment includes a first compound and the second dose or cycle of treatment includes a second compound that is different from the first compound.

35. The use of claim 20, wherein the medicament is to be administered, and whereby the subject is substantially relieved of at least one symptom within 3, 2, or 1 days; or 24, 20, 16, 12, 10, 8 hours or less of said administration.

36. The use of claim 20, wherein the subject is substantially relieved of at least one symptom for 1, 2, 3, 4, 5, 6, or 7 days; 1, 2, 3, or 4 weeks; or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more.

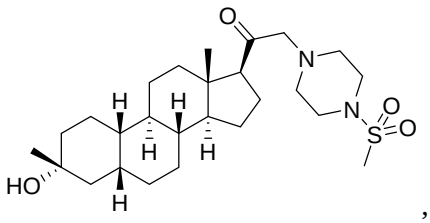
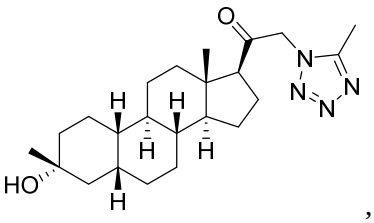
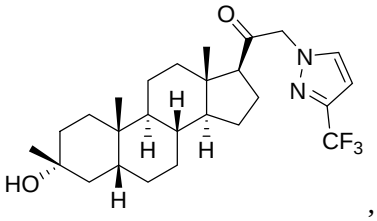
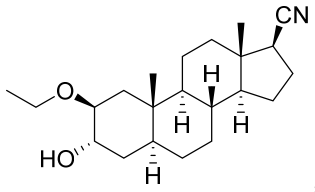
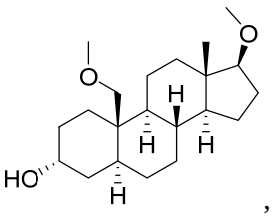
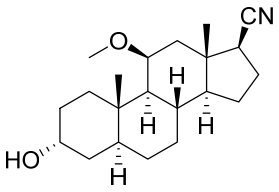
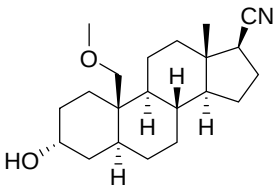
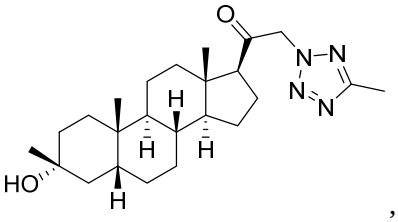
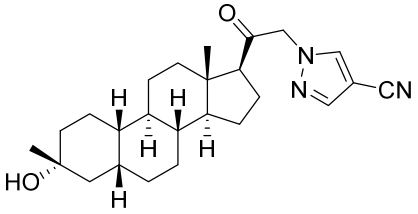
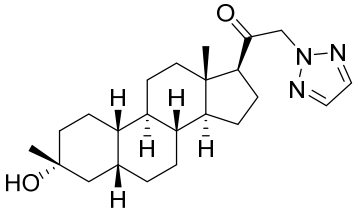
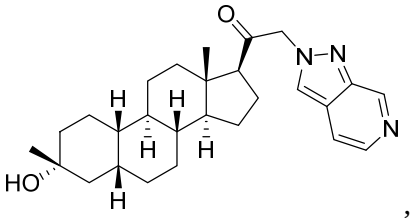
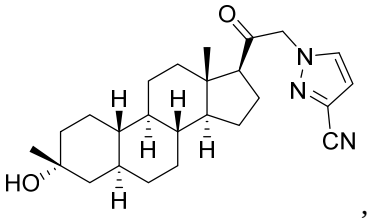
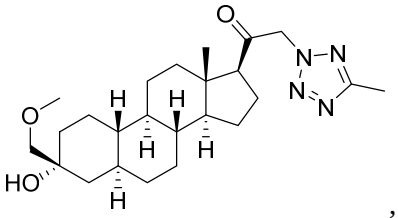
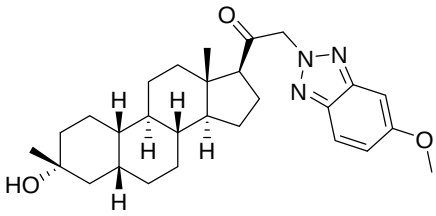
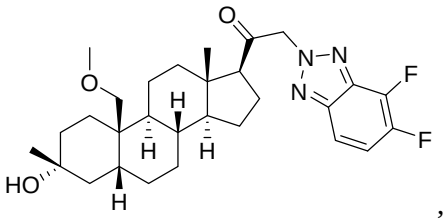
37. The use of claim 20, wherein the neuroactive steroid is selected from pregnanolone, ganaxolone, alphadalone, alphaxalone, and allopregnanolone.

38. The use of claim 20, wherein the neuroactive steroid is deuterated allopregnanolone.

39. The use of claim 20, wherein the neuroactive steroid is an estrol.

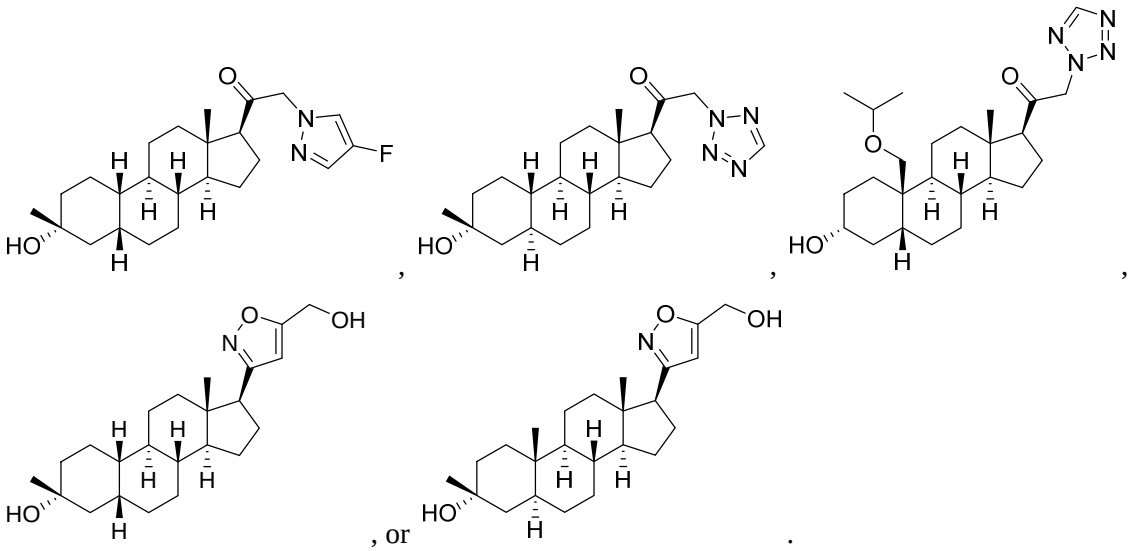
40. The use of claim 20, wherein the pharmaceutical composition is brexanolone.

41. The use of claim 20, wherein the neuroactive steroid is:


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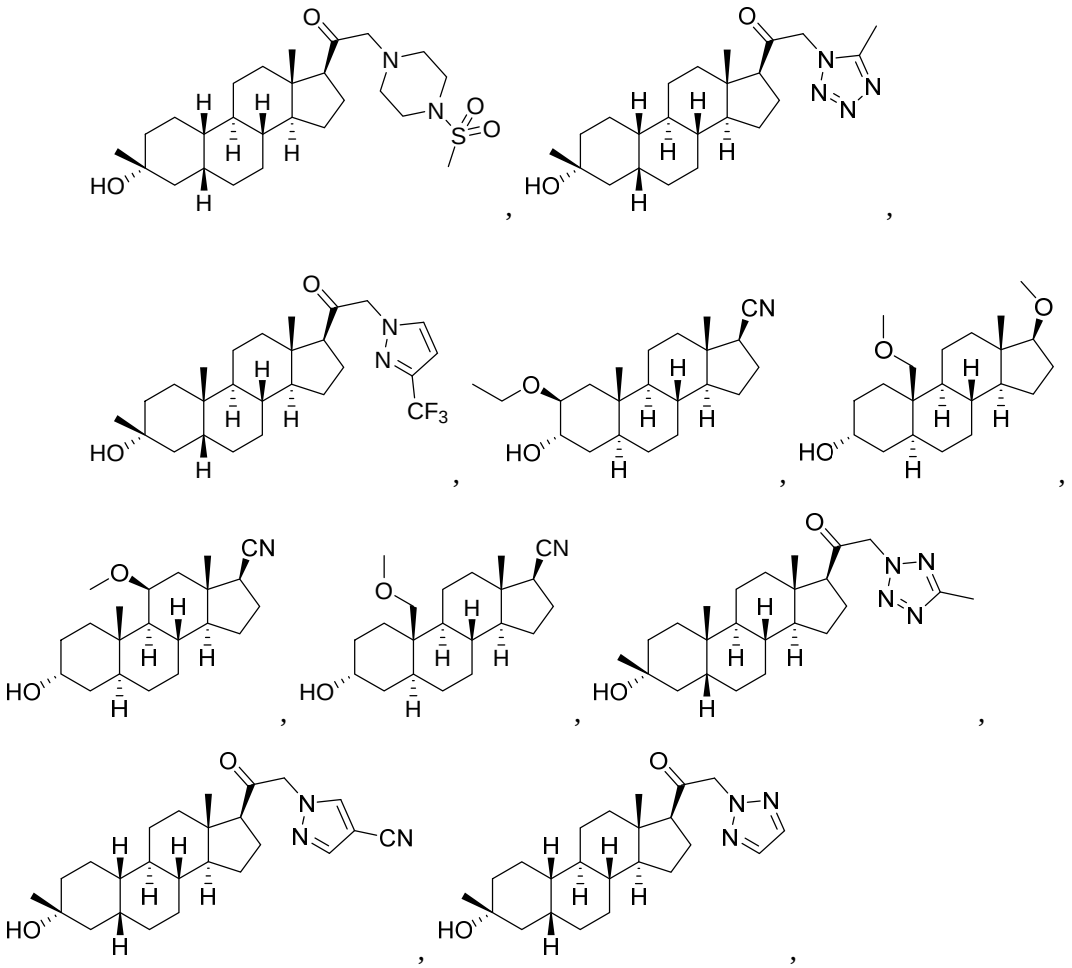
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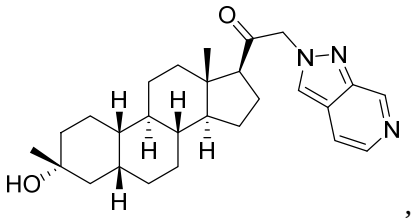
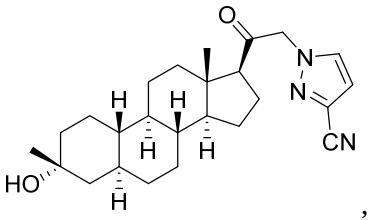
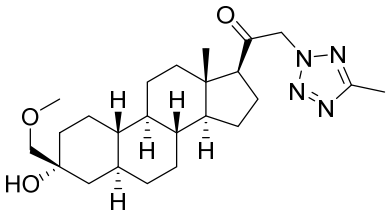
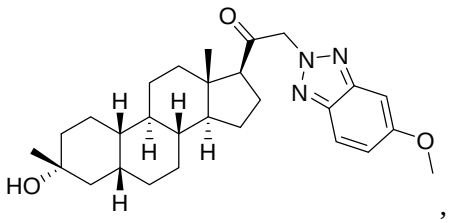
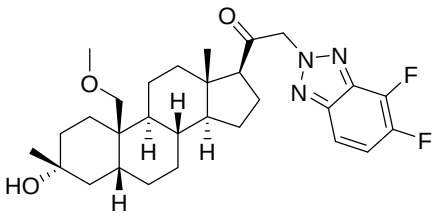
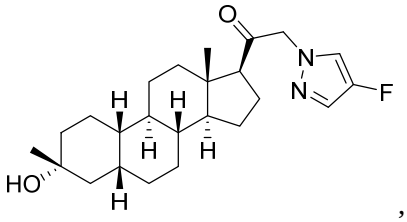
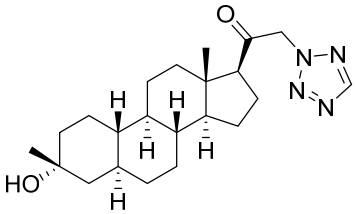
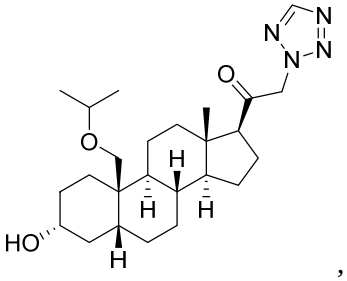
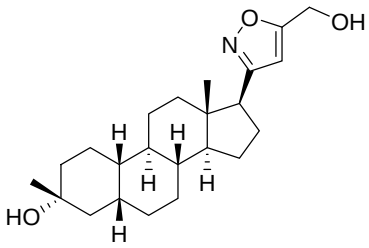
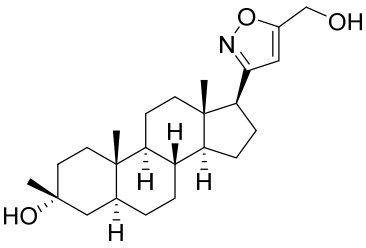
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, or .

42. The use of claim 20, wherein the pharmaceutically acceptable salt is a pharmaceutically acceptable salt of




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43. The use of claim 20, wherein the medicament is to be administered to the subject within 3 days, 2 days, 1 day, 24 hours of delivery of a baby.

44. The use of claim 20, wherein the subject is identified to be at a risk through a screening method.

45. The use of claim 20, wherein the subject has given birth.

46. The use of claim 20, wherein the subject is due to give birth.

47. The use of claim 46, wherein the subject is due to give birth in 9, 8, 7, 6, 5, 4, 3, 2, or 1 months; 4, 3, 2, or 1 weeks; or 7, 6, 5, 4, 3, 2, or 1 days.

48. The use of claim 20, wherein the subject has an attribute, characteristic, or exposure that increases the likelihood of developing depression.

49. The use of claim 48, wherein the subject has hyperemesis gravidarum.

50. The use of claim 48, wherein the subject has had a complication in pregnancy.

51. The use of claim 48, wherein the subject has had emotionally painful or stressful experiences around pregnancy, childbirth, or early parenting.

52. The use of claim 48, wherein the subject has had a history of domestic violence, sexual or other abuse.

53. The use of claim 48, wherein the subject has had a traumatic childhood.

54. The use of claim 48, wherein the subject has stress.

55. The use of claim 48, wherein the subject has lack of social support.

56. The use of claim 48, wherein the subject has a perfectionist or controlling personality.

57. The use of claim 20, wherein the subject is a female.

58. The use of claim 57, wherein the female is not breast feeding.

59. The use of claim 20, wherein the subject is an adult.

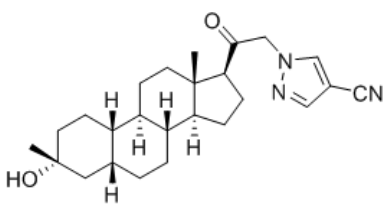
60. The use of claim 20, wherein the subject is from 18 to 45 years of age.

61. The use of claim 20, wherein the subject is suffering from postpartum depression.

62. The use of claim 20, wherein the subject has experienced a Major Depressive Episode in the postpartum period.

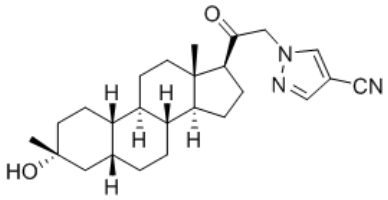
63. The use of claim 62, wherein the period begins within the first 4 weeks following delivery of a baby.

64. Use of Compound 9, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof in the manufacture of a medicament for treating a disorder described herein, wherein a total daily dose of said medicament of about 10 mg to about 100 mg is to be orally administered to a subject in need thereof.



(Compound 9)

65. Use of Compound 9 in the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder.



(Compound 9)