There is increasing evidence to support the role of neuroactive steroids in affective dysregulation. Evidence supports the use of neuroactive steroids, *e.g.,* progesterone and its metabolites; allopregnanolone, alphadalone, ganoxalone, alphaxolone, in the treatment and prevention of tremor (e.g., essential tremor), depression (e.g., postpartum depression), and anxiety disorder.

Summary

In one aspect, the present disclosure provides the use of a neuroactive steroid for the manufacture of a medicament to treat a human subject suffering from depression or an anxiety disorder.

In another aspect, the present disclosure provides the use of a neuroactive steroid for the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder, wherein the medicament is to administered as follows: administering a first infusion of a neuroactive steroid, wherein said first/step-up infusion is administered for 8-16 hours; administering a second/maintenance infusion of a neuroactive steroid, wherein said second/maintenance infusion is administered for 24-48 hours; and administering a third infusion of a neuroactive steroid, wherein said third/downward taper infusion is administered for 8-16 hours; said neuroactive steroid doses being sufficient to treat said subject.

In a further aspect, the present disclosure provides the use of a neuroactive steroid for the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder, wherein the medicament is to administered as follows: 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, or 15-70 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, or 86 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, or 15-70 μg/kg/hour; said neuroactive steroid doses being sufficient to treat said subject.

In another aspect, the present disclosure provides the use of a neuroactive steroid for the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder, wherein the medicament is to administered as follows: a) receiving information related to the therapeutic effect of a neuroactive steroid in reducing the depression or anxiety disorder in a subject

treated with the neuroactive steroid; and b) administering to the subject a therapeutic compound if the information indicates that the depression or anxiety disorder is reduced in the subject as compared to the subject before having received the neuroactive steroid, thereby treating the subject.

The disclosure features, *inter alia*, a method, the method comprising administering a neuroactive steroid, *e.g.,* pregnanolone, allopregnanolone, alphadalone, ganaxolone, or alphaxolone to a subject, for example to treat a CNS-related disorder such as tremor, depression, 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 an embodiment, the disclosure features a method of treating a human subject suffering from a movement disorder as described herein (e.g., tremor), the method comprising administering a therapeutically effective amount of a neuroactive steroid. In an embodiment, the disclosure features 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 method results in sedation. In some embodiments, the method provides therapeutic effect in the absence of sedative effect.

In some embodiments, the neuroactive steroid is pregnanolone, allopregnanolone, alphadalone, ganaxolone, or alphaxolone. In some embodiments, the neuroactive steroid is pregnanolone, allopregnanolone, alphadalone, ganaxolone, or alphaxolone. In some embodiments, the neuroactive steroid is allopregnanolone. In some embodiments, the neuroactive steroid is selected from neuroactive steroids that are disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181,

as allopregnanolone) and the second dose or cycle of treatment includes administering a second compound that is different from the first compound.

In some embodiments, the method comprises the steps of evaluating (e.g., diagnosing, prognosing, and determining a course of treatment in) a subject suffering from tremor (e.g., as described herein), comprising the steps of: a) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) in reducing tremor (e.g., the symptoms of tremor) in a subject treated with the neuroactive steroid (e.g., allopregnanolone); and b) determining if the tremor (e.g., the 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 an embodiment, the disclosure features a method of treating a subject suffering from tremor (*e.g.,* essential tremor), comprising: administering a first dose, wherein administration of said first dose 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 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. In some embodiments, the method results in sedation. In some embodiments, the method provides therapeutic effect in the absence of sedative effect.

In an embodiment, the disclosure features 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. In some embodiments, the method results in sedation. In some embodiments, the method provides therapeutic effect in the absence of sedative effect.

In an embodiment, the disclosure features 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 dayand 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 method results in sedation. In some embodiments, the method provides therapeutic effect in the absence of sedative effect.

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, 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, 24 hours, 2, 3, 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, 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, 24 hours, 2, 3, 4 days after the initiation of said third dose.

In an embodiment, provided herein is a method of prophylactically treating a disease or disorder described herein (e.g., tremor (e.g., essential tremor) in a human subject (e.g., as described herein, e.g., a subject identified as a subject at risk of suffering from a disease or disorder as described herein), 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 method results in sedation. In some embodiments, the method provides therapeutic effect in the absence of sedative effect.

In some embodiments, the method provides rapid onset of efficacy (e.g., rapid reduction in a symptom of tremor; rapidly affective to reduce a symptom of tremor, e.g., a subject experiences relief from a symptom of a tremor 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 tremor 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).

In some embodiments, the efficacy is maintained after a single course of treatment (e.g., single dose, multiple doses, or cycle of treatment) of a compound described herein (e.g., allopregnanolone).

In an embodiment, provided herein is 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) in reducing the tremor (e.g., symptoms of tremor) in a subject

treated with the neuroactive steroid (e.g., allopregnanolone); and b) administering to the subject a therapeutic compound (e.g., neuroactive steroid) if the information indicates that the tremor (e.g., symptoms of the tremor) is reduced in the subject as compared to the subject before having received the neuroactive steroid (e.g., allopregnanolone), thereby treating the subject.

In some embodiments, the therapeutic compound administered according to step a) is allopregnanolone. In some embodiments, the neuroactive steroid of step a) is administered by parenteral administration. In some embodiments, the therapeutic compound administered according to step b) is a different neuroactive steroid as the neuroactive steroid described in part a). In some embodiments, the therapeutic compound administered according to step b) is the same neuroactive steroid as the neuroactive steroid described in part a). In some embodiments, the therapeutic compound of step b) is allopregnanolone. In some embodiments, the neuroactive steroid of step b) is administered by parenteral administration. In some embodiments, the neuroactive steroid of step b) is administered by oral administration.

In some embodiments, the therapeutic compound administered according to step b) is selected from pregnanolone, ganaxolone, alphadalone, alphaxalone, and allopregnanolone. In some embodiments, the neuroactive steroid is allopregnanolone. In some embodiments, the neuroactive steroid is deuterated allopregnanolone. In some embodiments, the neuroactive steroid is an estrol. In some embodiments, the neuroactive steroid is selected from neuroactive steroids that are disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/10022, 8, U.S. Patent No. 5,232,917, US 8,575,375 and US 8,759,330.

In an embodiment, provided herein is a method of selecting a therapeutic compound (e.g., a neuroactive steroid) for treating tremor (e.g., essential tremor) in a human subject treated with a neuroactive steroid (e.g., allopregnanolone) comprising the steps of: a) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) in reducing the tremor (e.g., symptoms of the tremor) in a subject; and b) selecting the therapeutic compound (e.g., neuroactive steroid) if the information indicates that the tremor (e.g., symptoms of the tremor) is reduced in the subject as compared to the subject before having received the neuroactive steroid (e.g., allopregnanolone).

In some embodiments, the therapeutic compound administered according to step a) is allopregnanolone. In some embodiments, the neuroactive steroid of step a) is administered by parenteral administration. In some embodiments, the therapeutic compound administered according to step b) is a

different neuroactive steroid as the neuroactive steroid described in part a). In some embodiments, the therapeutic compound administered according to step b) is the same neuroactive steroid as the neuroactive steroid described in part a). In some embodiments, the therapeutic compound of step b) is allopregnanolone. In some embodiments, the neuroactive steroid of step b) is administered by parenteral administration. In some embodiments, the neuroactive steroid of step b) is administered by oral administration.

In some embodiments, the therapeutic compound administered according to step b) is selected from pregnanolone, ganaxolone, alphadalone, alphaxalone, and allopregnanolone. In some embodiments, the neuroactive steroid is allopregnanolone. In some embodiments, the neuroactive steroid is deuterated allopregnanolone. In some embodiments, the neuroactive steroid is an estrol. In some embodiments, the neuroactive steroid is selected from neuroactive steroids that are disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 and US 8,759,330.

In an embodiment, provided herein is a 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 the tremor) in a subject treated with the neuroactive steroid (e.g., allopregnanolone); and b) determining if the tremor (e.g., symptoms of the 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 compound is administered by oral administration. In some embodiments, the therapeutic compound is administered as a solid composition (e.g., a solid dosage form).

In an embodiment, where the evaluation shows that the treatment was effective (e.g., using a method described above), the method comprises administering to the subject a second neuoractive

steroid (e.g., wherein the second neuroactive steroid is different than the first neuroactive steroid). In an embodiment, the first neuroactive steroid is allopregnanolone. In an embodiment, the first neuroactive steroid is administered parenterally. In an embodiment, the first neuroactive steroid is administered orally. In some embodiments, the second neuroactive steroid is a different neuroactive steroid than the first neuroactive steroid (e.g., is a neuroactive steroid other than allopregnanolone). In some embodiments, the second neuroactive steroid is the same neuroactive steroid as the first neuroactive steroid (e.g., allopregnanolone). In some embodiments, the second neuroactive steroid is administered as an oral administration. In some embodiments, the second neuroactive steroid is administered parenterally. In some embodiments, the second neuroactive steroid is a compound disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 or US 8,759,330.

In an embodiment, provided herein is 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 compound (e.g., neuroactive steroid); and b) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) in reducing the tremor (e.g., symptoms of the 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.

In an embodiment, where the evaluation shows that the treatment was effective (e.g., using a method described above), the method comprises administering to the subject a second neuoractive steroid (e.g., wherein the second neuroactive steroid is different than the first neuroactive steroid). In an embodiment, the first neuroactive steroid is allopregnanolone. In an embodiment, the first neuroactive steroid is administered parenterally. In an embodiment, the first neuroactive steroid is administered orally. In some embodiments, the second neuroactive steroid is a different neuroactive steroid than the first neuroactive steroid (e.g., is a neuroactive steroid other than allopregnanolone). In some embodiments, the second neuroactive steroid is the same neuroactive steroid as the first neuroactive steroid (e.g., allopregnanolone). In some embodiments, the second neuroactive steroid is administered as an oral administration. In some embodiments, the second neuroactive steroid is administered parenterally. In some embodiments, the second neuroactive steroid is a compound disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832,

WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 or US 8,759,330.

In an embodiment, the disclosure features a method for treating a human subject suffering from depression (*e.g.,* postpartum depression) or an anxiety disorder, the method comprising administering a therapeutically effective amount of a neuroactive steroid. In some embodiments, the subject is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

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).

In some embodiments, the efficacy is maintained after a single course of treatment (e.g., single dose, multiple doses, or cycle of treatment) of a compound described herein (e.g., allopregnanolone).

In some embodiments, the neuroactive steroid is pregnanolone, allopregnanolone, alphadalone, ganaxolone, or alphaxolone. In some embodiments, the neuroactive steroid is allopregnanolone. In some embodiments, the neuroactive steroid is selected from neuroactive steroids that are disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 and US 8,759,330.

In some embodiments, the depression is clinical depression (also known as major depression, major depressive disorder, severe depression, unipolar depression, unipolar disorder, or recurrent 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 perinatal depression.

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

In some embodiments, the subject is a female. 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. In some embodiments, the subject has been identified as being at risk of depression (e.g., postpartum depression), for example by a method of evaluation as described herein. In some embodiments, the subject is in her third trimester of pregnancy. In some embodiments, the subject is suffering from perinatal depression. In some embodiments, the subject has reducded levels of allopregnanolone relative to a reference standard (e.g., relative to the level of allopregnanolone in a subject does not later suffer from depression (e.g., postpartum depression, perinatal depression).

In an embodiment, the method comprises administering a second neuroactive steroid. In an embodiment, the first neuroactive steroid is allopregnanolone. In an embodiment, the first neuroactive steroid is administered parenterally. In some embodiments, the second neuroactive steroid a different neuroactive steroid than the first neuroactive steroid (e.g., is a neuroactive steroid other than allopregnanolone). In some embodiments, the second neuroactive steroid is administered as an oral administration.

In an embodiment, the disclosure features a method for treating a human subject suffering from depression (e.g., postpartum depression) or an anxiety disorder, the method comprising administering to the subject a therapeutically effective amount of a neuroactive steroid (e.g., allopregnanolone). In some embodiments, the administration is intravenous administration. In some embodiments, the administration is oral administration. In some embodiments, the subject is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

In some embodiments, the method provides maintenance treatment or preventative treatment.

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 acute treatment

In some embodiments, the administering comprises administering a plurality of infusions. In some embodiments, the administering comprises administering a first, second, and third infusion. In some embodiments, the administration of the second infusion begins no longer than 90, 60, 30, 10, or 5 minutes after the beginning or end of the administration of the first infusion. In some embodiments, the second infusion begins 0 to 90, 0 to 60, 0 to 30, 0 to 10, or 0 to 5 minutes after the beginning or end of the administration of the first infusion. In some embodiments, the second infusion begins no more than 60, 30, 20, 10, 5, 4, 3, 2, 1 minute after the end of administration of the first infusion. In some embodiments, the second infusion begins at the end of administration of the first infusion. In some embodiments, the first infusion and the initiation of the second infusion are performed with the same delivery device, *e.g.,* with the same cannula or reservoir.

In some embodiments, the amount of neuroactive steroid delivered/unit time varies during the first infusion. In some embodiments, the first (step-up) infusion delivers a smaller amount of neuroactive steroid/unit time than the second (maintenance) infusion. In some embodiments, the first (step-up) infusion comprises administering a plurality of step doses, wherein each subsequent step dose delivers a larger amount of neuroactive steroid/unit time than the step dose that precedes it. In some embodiments, the third infusion is administered for a period of time that is between 5 and 20 hours, 8 and 16 hours, 10 and 15 hours, or 10 and 13 hours. In some embodiments, the first infusion is administered for 12 +/- 2 hours. In some embodiments, the first infusion is administered for 12 hours. In some embodiments, the amount of neuroactive steroid delivered/unit time varies during the first infusion. In some embodiments, administering said step-up dose comprises administering a continuously increasing amount of neuroactive steroid. In some embodiments, administering said step-up dose comprises administering a continuously increasing amount of neuroactive steroid/unit time.

In some embodiments, the administration comprises a first, second, and third step dose. In some embodiments, said first step dose is administered at an amount of neuroactive steroid/unit time of 5-50 μg/kg/hour (*e.g.,* 21.5 μg/kg/hour). In some embodiments, said first step dose is administered at an amount of neuroactive steroid/unit time of 5-50 μg/kg/hour, 10-40 μg/kg/hour, 20-30 μg/kg/hour, 20 μg/kg/hour, 21 μg/kg/hour, 22 μg/kg/hour, or 21.5 μg/kg/hour. In some embodiments, said second step dose is administered at an amount of neuroactive steroid/unit time of 10-100 μg/kg/hour (*e.g.,* 43 μg/kg/hour). In some embodiments, said second step dose is administered at an amount of neuroactive steroid/unit time of 10-100 μg/kg/hour, 20-70 μg/kg/hour, 30-50 μg/kg/hour, 42 μg/kg/hour, 43 μg/kg/hour, or 44 μg/kg/hour. In some embodiments, said third step dose is administered at an amount of neuroactive steroid/unit time of 25-150 μg/kg/hour. In some embodiments, said third step dose is administered at an amount of neuroactive steroid/unit time of 25-150 μg/kg/hour, 40-100 μg/kg/hour, 60-

70 μg/kg/hour, 63 μg/kg/hour, 64 μg/kg/hour, 65 μg/kg/hour, or 64.5 μg/kg/hour. In some embodiments, said first step dose is 10 to 40% (*e.g.*, 25%) of the second/maintenance infusion; said second step dose is 30 to 70% (*e.g.*, 50%) of the second/maintenance infusion; and said third step dose is 60 to 90% (*e.g.*, 75%) of the second/maintenance infusion. In some embodiments, the amount of neuroactive steroid delivered/unit time in said first step dose is 10 to 40% (*e.g.*, 25%) of the amount of neuroactive steroid delivered/unit time in said second/maintenance infusion; the amount of neuroactive steroid delivered/unit time in said second step dose is 30 to 70% (*e.g.*, 50%) of the amount of neuroactive steroid delivered/unit time in said second/maintenance infusion; and the amount of neuroactive steroid delivered/unit time in said third step dose is 60 to 90% (*e.g.*, 75%) of the amount of neuroactive steroid delivered/unit time in said second/maintenance infusion.

In some embodiments, the third (step-down/downward taper) infusion delivers a smaller amount of neuroactive steroid/unit time than the second (maintenance) infusion. In some embodiments, the third (step-down/downward taper) infusion comprises administering a plurality of step doses, wherein each subsequent step dose delivers a lower amount of neuroactive steroid/unit time than the step dose that precedes it. In some embodiments, said third infusion is administered for a period of time that is between 5 and 20 hours, 8 and 16 hours, 10 and 15 hours, or 10 and 13 hours. In some embodiments, said third infusion is administered for 12 +/- 2 hours. In some embodiments, said third infusion is administered for 12 hours. In some embodiments, administering said downward taper dose comprises administering a continuously decreasing amount of neuroactive steroid. In some embodiments, administering said downward taper dose comprises administering a continuously decreasing amount of neuroactive steroid/unit time.

In some embodiments, the administration comprises a first, second, and third step dose. In some embodiments, said first step dose is administered at an amount of neuroactive steroid/unit time of 15-150 μg/kg/hour. In some embodiments, said first step dose is administered at an amount of neuroactive steroid/unit time of 15-150 μg/kg/hour, 40-100 μg/kg/hour, 60-70 μg/kg/hour, 63 μg/kg/hour, 64 μg/kg/hour, 65 μg/kg/hour, or 64.5 μg/kg/hour. In some embodiments, said second step dose is administered at an amount of neuroactive steroid/unit time of 10-100 μg/kg/hour(*e.g.*, 43 μg/kg/hour). In some embodiments, said second step dose is administered at an amount of neuroactive steroid/unit time of 10-100 μg/kg/hour, 20-70 μg/kg/hour, 30-50 μg/kg/hour, 42 μg/kg/hour, 43 μg/kg/hour, or 44 μg/kg/hour. In some embodiments, said third step dose is administered at an amount of neuroactive steroid/unit time of 5-50 μg/kg/hour (*e.g.*, 21.5 μg/kg/hour). In some embodiments, said third step dose is administered at an amount of neuroactive steroid/unit time of 5-50 μg/kg/hour, 10-40 μg/kg/hour, 20-30 μg/kg/hour, 20 μg/kg/hour, 21 μg/kg/hour, 22 μg/kg/hour, or 21.5 μg/kg/hour.

In some embodiments, said first step dose is 60 to 90% (*e.g.*, 75%) of the second/maintenance infusion; said second step dose is 30 to 70% (*e.g.*, 50%) of the second/maintenance infusion; and said third step dose is 10 to 40% (*e.g.*, 25%) of the second/maintenance infusion.

In some embodiments, the amount of neuroactive steroid delivered/unit time in said first step dose is 60 to 90% (*e.g.*, 75%) of the amount of neuroactive steroid delivered/unit time in said second/maintenance infusion; the amount of neuroactive steroid delivered/unit time in said second step dose is 30 to 70% (*e.g.*, 50%) of the amount of neuroactive steroid delivered/unit time in said second/maintenance infusion; and the amount of neuroactive steroid delivered/unit time in said third step dose is 10 to 40% (*e.g.*, 25%) of the amount of neuroactive steroid delivered/unit time in said second/maintenance infusion.

In some embodiments, the method comprises administering a second/maintenance infusion of 50-150 μg/kg/hour (*e.g.*, 86 μg/kg/hour) of the neuroactive steroid. In some embodiments, the second/maintenance infusion is 50-150 μg/kg/hour, 60-100 μg/kg/hour, 70-90 μg/kg/hour, 85 μg/kg/hour, 86 μg/kg/hour, or 87 μg/kg/hour. In some embodiments, said second/maintenance infusion is administered for a period of time that is between 5 and 80 hours, 10 and 70 hours, 20 and 50 hours, or 30 and 40 hours. In some embodiments, said second/maintenance infusion is administered for 36+/-5 hours. In some embodiments, said second/maintenance infusion is administered for 36 hours.

In some embodiments, the plasma concentration of said second/maintenance infusion is measured at a preselected time, *e.g.*, at 10, 15, 20, 30, 45, 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, 24 hours, 2, 3, 4 days after the initiation of said second/maintenance infusion. In some embodiments, said second/maintenance infusion results in a plasma concentration of 150 nM, *e.g.*, as measured at a preselected time, *e.g.*, at 10, 15, 20, 30, 45, 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, 24 hours, 2, 3, 4 days after the initiation of said second/maintenance infusion. In some embodiments, said second/maintenance infusion is administered at the same amount of neuroactive steroid/unit time over the entire second/maintenance infusion.

In an embodiment, the method comprises administering a second neuroactive steroid. In an embodiment, the first neuroactive steroid is allopregnanolone. In an embodiment, the first neuroactive steroid is administered parenterally (e.g., as described in the embodiments above). In some embodiments, the second neuroactive steroid a different neuroactive steroid than the first neuroactive steroid (e.g., is a neuroactive steroid other than allopregnanolone). In some embodiments, the second neuroactive steroid is administered as an oral administration (orally).

In an embodiment, the disclosure features 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 suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

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).

In some embodiments, the efficacy is maintained after a single course of treatment (e.g., single dose, multiple doses, or cycle of treatment) of a compound described herein (e.g., allopregnanolone).

In an embodiment, the disclosure features 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, 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, or 15-70 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, or 86 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, or 15-70 μg/kg/hour; said neuroactive steroid doses being sufficient to treat said subject.

In some embodiments, the subject is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

In some embodiments, the depression is clinical depression (also known as major depression, major depressive disorder, severe depression, unipolar depression, unipolar disorder, or recurrent 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 perinatal depression.

In an embodiment, the method comprises administering a second neuroactive steroid. In an embodiment, the first neuroactive steroid is allopregnanolone. In an embodiment, the first neuroactive steroid is administered parenterally. In some embodiments, the second neuroactive steroid a different neuroactive steroid than the first neuroactive steroid (e.g., is a neuroactive steroid other than allopregnanolone). In some embodiments, the second neuroactive steroid is administered as an oral administration. In some embodiments, the second neuroactive steroid is a compound disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 or US 8,759,330.

In an embodiment, provided herein is 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) 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); and b) administering to the subject a therapeutic compound (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), thereby treating the subject.

In some embodiments, the subject is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

In some embodiments, the therapeutic compound administered according to step a) is allopregnanolone. In some embodiments, the neuroactive steroid of step b) is administered by parenteral administration. In some embodiments, the administering step (e.g., the administering step of step b) is

oral administration. In some embodiments, the therapeutic compound administered according to step b) is a different neuroactive steroid as the neuroactive steroid described in part a).

In some embodiments, the therapeutic compound administered according to step b) is selected from pregnanolone, ganaxolone, alphadalone, alphaxalone, and allopregnanolone. In some embodiments, the neuroactive steroid is allopregnanolone. In some embodiments, the neuroactive steroid is deuterated allopregnanolone. In some embodiments, the neuroactive steroid is an estrol. In some embodiments, the neuroactive steroid is selected from neuroactive steroids that are disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 and US 8,759,330.

In some embodiments, the information related to therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) is measured by reduction in HAM-D, EPDS, CGI, or GAD-7.

In an embodiment, provided herein is a method of selecting a therapeutic compound (e.g., a neuroactive steroid) for treating depression or an anxiety disorder in a human subject treated with a neuroactive steroid (e.g., allopregnanolone) comprising the steps of: a) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) in reducing the depression or anxiety disorder (e.g., symptoms of the depression or anxiety disorder) in a subject; and b) selecting the therapeutic compound (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).

In some embodiments, the subject is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

In some embodiments, the therapeutic compound administered according to step a) is allopregnanolone. In some embodiments, the neuroactive steroid of step b) is administered by parenteral administration. In some embodiments, the administering step (e.g., the administering step of step b) is oral administration. In some embodiments, the therapeutic compound administered according to step b) is a different neuroactive steroid as the neuroactive steroid described in part a).

In some embodiments, the therapeutic compound administered according to step b) is selected from pregnanolone, ganaxolone, alphadalone, alphaxalone, and allopregnanolone. In some embodiments,

the neuroactive steroid is allopregnanolone. In some embodiments, the neuroactive steroid is deuterated allopregnanolone. In some embodiments, the neuroactive steroid is an estrol. In some embodiments, the neuroactive steroid is selected from neuroactive steroids that are disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 and US 8,759,330.

In some embodiments, the information related to therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) is measured by reduction in HAM-D, EPDS, CGI, or GAD-7.

In an embodiment, provided herein is a method of evaluating (e.g., diagnosing, prognosing, and determining a course of treatment in) 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) 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); 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 is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

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

In some embodiments, the information related to therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) is measured by reduction in HAM-D, EPDS, CGI, or GAD-7.

In an embodiment, where the evaluation shows that the treatment was effective (e.g., using a method described above), the method comprises administering to the subject a second neuoractive steroid (e.g., wherein the second neuroactive steroid is different than the first neuroactive steroid). In an embodiment, the first neuroactive steroid is allopregnanolone. In an embodiment, the first neuroactive steroid is administered parenterally. In some embodiments, the second neuroactive steroid a different neuroactive steroid than the first neuroactive steroid (e.g., is a neuroactive steroid other than allopregnanolone). In some embodiments, the second neuroactive steroid is administered as an oral administration. In some embodiments, the second neuroactive steroid is a compound disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 or US 8,759,330.

In an embodiment, provided herein is a method of evaluating (e.g., diagnosing, prognosing, or determining a course of treatment in) a subject suffering from depression or an anxiety disorder, comprising the steps of: a) administering to the subject a therapeutic compound (e.g., neuroactive steroid); and b) receiving information related to the therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) 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), thereby evaluating the subject.

In some embodiments, the subject is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

In some embodiments, the information related to therapeutic effect of a neuroactive steroid (e.g., allopregnanolone) is measured by reduction in HAM-D, EPDS, CGI, or GAD-7.

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.

In an embodiment, where the evaluation shows that the treatment was effective (e.g., using a method described above), the method comprises administering to the subject a second neuoractive steroid (e.g., wherein the second neuroactive steroid is different than the first neuroactive steroid). In an embodiment, the first neuroactive steroid is allopregnanolone. In an embodiment, the first neuroactive steroid is administered parenterally. In some embodiments, the second neuroactive steroid a different

neuroactive steroid than the first neuroactive steroid (e.g., is a neuroactive steroid other than allopregnanolone). In some embodiments, the second neuroactive steroid is administered as an oral administration. In some embodiments, the second neuroactive steroid is a compound disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 or US 8,759,330.

In an embodiment, provided herein is a 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. In some embodiments, the concentrations of allopregnanolone in plasma is greater than that in a normal subject (e.g., a subject not suffering from a neuroendocrine disease (or neuroendocrine dysfunction). In some embodiments, the concentrations of allopregnanolone in plasma is 10 nM in plasma or less.

In some embodiments, the neuroactive steroid is selected from pregnanolone, ganaxolone, alphadalone, alphaxalone, and allopregnanolone. In some embodiments, the neuroactive steroid is allopregnanolone. In some embodiments, the neuroactive steroid is deuterated allopregnanolone. In some embodiments, the neuroactive steroid is an estrol. In some embodiments, the neuroactive steroid is selected from neuroactive steroids that are disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 and US 8,759,330.

In an embodiment, provided herein is a 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.

In an embodiment, provided herein is a 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.

In an embodiment, provided herein is a method of prophylactically treating a disease or disorder described herein (e.g., depression (e.g., postpartum depression) or an anxiety disorder) in a human subject (e.g., as described herein, e.g., a subject identified as a subject at risk of suffering from a disease or disorder as described herein), the method comprising administering a therapeutically effective amount of a neuroactive steroid.

In some embodiments, the subject is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

In some embodiments, the neuroactive steroid is pregnanolone, allopregnanolone, alphadalone, ganaxolone, or alphaxolone. In some embodiments, the neuroactive steroid is selected from pregnanolone, ganaxolone, alphadalone, alphaxalone, and allopregnanolone. In some embodiments, the neuroactive steroid is allopregnanolone. In some embodiments, the neuroactive steroid is deuterated allopregnanolone. In some embodiments, the neuroactive steroid is an estrol. In some embodiments, the neuroactive steroid is selected from neuroactive steroids that are disclosed in WIPO Publication Nos. WO2013/188792, WO 2013/056181, WO2015/010054, WO2014/169832, WO2014/169836, WO2014/169833, WO2014/169831, WO2015/027227, WO 2014/100228, U.S. Patent No. 5,232,917, US 8,575,375 and US 8,759,330.In some embodiments, the subject is identified as being at risk of suffering from a disease or disorder as described herein In some embodiments, the subject has been identified as being at risk of depression (e.g., postpartum depression) or an anxiety disorder, for example by a method of evaluation as described herein. . In some embodiments, the subject is identified based upon information related to therapeutic effect of a neuroactive steroid (e.g., allopregnanolone). In some embodiments, the information is measured by reduction in HAM-D, EPDS, CGI, or GAD-7. In some embodiments, the subject is in her third trimester of pregnancy. In some embodiments, the subject is suffering from perinatal depression. In some embodiments, the subject has reducded levels of allopregnanolone relative to a reference standard (e.g., relative to the level of allopregnanolone in a subject does not later suffer from depression (e.g., postpartum depression, perinatal depression).

In an embodiment, the neuroactive steroid is provided in a composition comprising a cyclodextrin, *e.g.,* β-cyclodextrin, *e.g.,* sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL. In some embodiments, the neuroactive steroid is provided at a concentration of 0.1 to 10 mg/mL neuroactive steroid. In some embodiments, the neuroactive steroid is provided at a concentration of 0.1, 0.5, 1, 1.25, 2.5, 3.75, 5, 6.25, 7.5, 8, 9, or 10 mg/mL neuroactive steroid. In some embodiments, the neuroactive steroid is provided at a concentration of 1.25 mg/mL neuroactive steroid. In some embodiments, the neuroactive steroid is

provided at a concentration of 2.5 mg/mL neuroactive steroid. In some embodiments, the neuroactive steroid is provided at a concentration of 3.75 mg/mL neuroactive steroid. In some embodiments, the neuroactive steroid is provided at a concentration of 5 mg/mL neuroactive steroid. In some embodiments, the cyclodextrin is present in the composition at 1-30%, 2-18%, 10-15% by weight of cyclodextrin per volume of composition. In some embodiments, the cyclodextrin is present in the composition at 1, 2.5, 5, 10, 12, 13, 15, 30% by weight of cyclodextrin per volume of composition. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition. In some embodiments, the cyclodextrin is present in the composition at 1-30%, 2-18%, 10-15% by weight of cyclodextrin per volume of composition and the neuroactive steroid is provided at a concentration of 0.1, 0.5, 1, 1.25, 2.5, 3.75, 5, 6.25, 7.5, 8, 9, or 10 mg/mL neuroactive steroid. In some embodiments, the cyclodextrin is present in the composition at 1, 2.5, 5, 10, 12, 13, 15, 30% by weight of cyclodextrin per volume of composition and the neuroactive steroid is provided at a concentration of 0.1, 0.5, 1, 1.25, 2.5, 3.75, 5, 6.25, 7.5, 8, 9, or 10 mg/mL neuroactive steroid. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the neuroactive steroid is provided at a concentration of 5 mg/mL neuroactive steroid. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the neuroactive steroid is provided at a concentration of 3.75 mg/mL neuroactive steroid. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the neuroactive steroid is provided at a concentration of 2.5 mg/mL neuroactive steroid. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the neuroactive steroid is provided at a concentration of 1.25 mg/mL neuroactive steroid.

In another embodiment, the disclosure features a composition, the composition comprising a neuroactive steroid, *e.g.*, pregnanolone, allopregnanolone, alphadalone, ganaxolone, or alphaxolone; and cyclodextrin, *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®, complex. 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®, complex.

In some embodiments, the neuroactive steroid is a progestin derivative, *e.g.*, pregnanolone, allopregnanolone, alphadalone, ganaxolone, or alphaxolone. In an embodiment, the neuroactive steroid is allopregnanolone. In an embodiment, the neuroactive steroid is ganaxolone. In an embodiment, the neuroactive steroid is alphaxolone. In some embodiments, the neuroactive steroid is selected from

In one embodiment, the disclosure features a composition, the composition comprising a neuroactive steroid, *e.g.,* pregnanolone, allopregnanolone, alphadalone, ganaxolone, alphaxolone; and 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®, complex, wherein the composition comprises less than 100ppm of a phosphate, and the 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®, has an absorption of less than 0.2 A.U. due to a drug-degrading agent, as determined by UV/vis spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution comprising 300 mg of the 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®, per mL of solution in a cell having a 1cm path length.

In some embodiments, the 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®, has an absorption of less than 0.2 A.U. due to a color forming agent, as determined by UV/vis spectrophotometry at a wavelength of 320 nm to 350 nm for an aqueous solution comprising 500 mg of the 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®, per mL of solution in a cell having a 1cm path length.

In some embodiments, the 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®, further comprises: less than 20 ppm of a sulfoalkylating agent; less than 0.5% wt. of an underivatized cyclodextrin; less than 1% wt. of an alkali metal halide salt; and less than 0.25% wt. of a hydrolyzed sulfoalkylating agent.

In some embodiments, the 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®, has an absorption of less than 0.2 A.U. due to a drug-degrading agent, as determined by UV/vis spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution comprising 500 mg of the 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®, per mL of solution in a cell having a 1 cm path length.

In some embodiments, the 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®, further comprises: less than 50 ppm of a phosphate; less than 10 ppm of a sulfoalkylating agent; less than 0.2%

e.g., a sulfo butyl ether β-cyclodextrin, *e.g.*, a β-cyclodextrin, *e.g.*, a sulfo butyl ether β-cyclodextrin, *e.g.*, CAPTISOL®, is formulated as an aqueous composition with a pH about 6.

In an embodiment, the disclosure features a kit comprising one or more of: a preparation of neuroactive steroid, *e.g.*, a plurality of preparations of neuroactive steroid at concentrations suitable for use at the first, second, and third dosages; and instructions for use for treating a subject suffering from tremor (*e.g.*, essential tremor).

In an embodiment, the disclosure features a kit comprising one or more of: a preparation of neuroactive steroid, *e.g.*, a plurality of preparations of neuroactive steroid at concentrations suitable for use at the first, second, and third infusions; and instructions for use for treating a subject suffering from depression (*e.g.*, postpartum depression) or an anxiety disorder.

In some embodiments, the subject is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

In an embodiment, the disclosure features a method of adjusting the amount of diluents and or neuroactive steroid flowing into or out of a delivery device, *e.g.*, a catheter, reservoir, the method comprising altering, *e.g.*, decreasing, the flow rate of neuroactive steroid flowing into the delivery device, so as to release in succession, two or more of a first dose, a second dose and one or more step doses of the third dose.

In some embodiments, the subject is suffering from an anxiety disorder. In some embodiments, the subject is suffering from depression. In some embodiments, the subject is suffering from postpartum depression.

Definitions

Chemical definitions

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*,

Claims

1. Use of a neuroactive steroid for the manufacture of a medicament to treat a human subject suffering from depression or an anxiety disorder.

2. The use of claim 1, 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.

3. The use of claim 1, wherein the depression is severe depression.

4. The use of claim 1, wherein the depression is postpartum depression.

5. The use of claim 1, wherein the use provides acute treatment of the depression.

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

7. The use of claim 1, wherein the neuroactive steroid is allopregnanolone.

8. The use of claim 1, wherein the neuroactive steroid is deuterated allopregnanolone.

9. The use of claim 1, wherein the subject is suffering from postpartum depression.

10. The use of claim 1, wherein the infusion is a continuous infusion.

11. The use of claim 1, wherein the use comprises administering a plurality of infusions.

12. The use of claim 11, comprising administering a first, second, and third infusion.

13. The use of claim 12, wherein the first (step-up) infusion comprises administering a plurality of step doses, wherein each subsequent step dose delivers a larger amount of neuroactive steroid/unit time than the step dose that precedes it.

14. The use of claim 13, wherein administering said step-up dose comprises administering a continuously increasing amount of neuroactive steroid/unit time.

15. The use of claim 13, comprising a first, second, and third step dose.

16. The use of claim 15, said first step dose is administered at an amount of neuroactive steroid/unit time of 5-50 μg/kg/hour, 10-40 μg/kg/hour, 20-30 μg/kg/hour, 20 μg/kg/hour, 21 μg/kg/hour, 22 μg/kg/hour, or 21.5 μg/kg/hour.

17. The use of claim 15, said second step dose is administered at an amount of neuroactive steroid/unit time of 10-100 μg/kg/hour, 20-70 μg/kg/hour, 30-50 μg/kg/hour, 42 μg/kg/hour, 43 μg/kg/hour, or 44 μg/kg/hour.

18. The use of claim 15, wherein the third (step-down/downward taper) infusion comprises administering a plurality of step doses, wherein each subsequent step dose delivers a lower amount of neuroactive steroid/unit time than the step dose that precedes it.

19. The use of claim 18, comprising a first, second, and third step dose.

20. The use of claim 19, said first step dose is administered at an amount of neuroactive steroid/unit time of 25-150 μg/kg/hour, 40-100 μg/kg/hour, 60-70 μg/kg/hour, 63 μg/kg/hour, 64 μg/kg/hour, 65 μg/kg/hour, or 64.5 μg/kg/hour.

21. The use of claim 19, said second step dose is administered at an amount of neuroactive steroid/unit time of 10-100 μg/kg/hour, 20-70 μg/kg/hour, 30-50 μg/kg/hour, 42 μg/kg/hour, 43 μg/kg/hour, or 44 μg/kg/hour.

22. The use of claim 19, said third step dose is administered at an amount of neuroactive steroid/unit time of 5-50 μg/kg/hour, 10-40 μg/kg/hour, 20-30 μg/kg/hour, 20 μg/kg/hour, 21 μg/kg/hour, 22 μg/kg/hour, or 21.5 μg/kg/hour.

23. The use of claim 12, wherein the use comprises administering a second/maintenance infusion of 50-150 μg/kg/hour of the neuroactive steroid.

24. The use of claim 12, wherein the second/maintenance infusion is 50-150 μg/kg/hour, 60-100 μg/kg/hour, 70-90 μg/kg/hour, 85 μg/kg/hour, 86 μg/kg/hour, or 87 μg/kg/hour.

25. Use of a neuroactive steroid for the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder, wherein the medicament is to administered as follows:

administering a first infusion of a neuroactive steroid, wherein said first/step-up infusion is administered for 8-16 hours;

administering a second/maintenance infusion of a neuroactive steroid, wherein said second/maintenance infusion is administered for 24-48 hours; and

administering a third infusion of a neuroactive steroid, wherein said third/downward taper infusion is administered for 8-16 hours;

said neuroactive steroid doses being sufficient to treat said subject.

26. Use of a neuroactive steroid for the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder, wherein the medicament is to administered as follows:

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, or 15-70 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, or 86 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, or 15-70 μg/kg/hour;

said neuroactive steroid doses being sufficient to treat said subject.

27. The use of claim 1, wherein the neuroactive steroid is provided in a composition comprising a cyclodextrin.

28. The use of claim 1, wherein the neuroactive steroid is provided at a concentration of 0.1 to 10 mg/mL neuroactive steroid.

29. The use of claim 1, wherein the neuroactive steroid is provided at a concentration of 0.1, 0.5, 1, 1.25, 2.5, 3.75, 5, 6.25, 7.5, 8, 9, or 10 mg/mL neuroactive steroid.

30. The use of claim 27, wherein the cyclodextrin is present in the composition at 1-30%, 2-18%, 10-15% by weight of cyclodextrin per volume of composition.

31. Use of a neuroactive steroid for the manufacture of a medicament for treating a human subject suffering from depression or an anxiety disorder, wherein the medicament is to administered as follows:

a) receiving information related to the therapeutic effect of a neuroactive steroid in reducing the depression or anxiety disorder in a subject treated with the neuroactive steroid; and

b) administering to the subject a therapeutic compound if the information indicates that the depression or anxiety disorder is reduced in the subject as compared to the subject before having received the neuroactive steroid,

thereby treating the subject.

32. The use of claim 31, wherein the subject has been administered the neuroactive steroid by intravenous infusion.

33. The use of claim 31, wherein the therapeutic compound is administered by oral administration.

34. The method of claim 33, wherein the therapeutic compound is administered as a solid composition.

35. The use of claim 1, wherein the depression is major depressive disorder.