METHODS OF TREATING EPILEPSY OR STATUS EPILEPTICUS

Claims of Priority

This application claims priority to U.S.S.N. 61/691,545, filed August 21, 2012 and U.S.S.N. 61/789,491, filed March 15, 2013, the entire contents of which are incorporated herein by reference.

Field of the Invention

The present invention generally relates to methods of treating epilepsy or status epilepticus by administering a neuroactive steroid.

Summary ~~of the Invention~~

Described herein are methods of treating epilepsy or status epilepticus.*e.g.,* convulsive status epilepticus, *e.g.,* early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus; non-convulsive status epilepticus, *e.g.,* generalized status epilepticus, complex partial status epilepticus; generalized periodic epileptiform discharges; periodic lateralized epileptiform discharges; a seizure, *e.g.,* acute repetitive seizures, cluster seizures, the method comprising administering to the subject a neuroactive steroid. In one ~~aspect~~embodiment, the ~~invention~~ present disclosure features a method of treating a subject having epilepsy or status epilepticus by administering in combination to the subject a neuroative steroid and a benzodiazepine. In some embodiments, the method further comprises administering at least one of the neuroative steroid or benzodiazepine parenterally (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly). In some embodiments, both the neuroative steroid and benzodiazepine are administered parenterally.

In some embodiments, the neuroative steroid and benzodiazepine are co-administered (*e.g.,* administered simultaneously). In some embodiments, the neuroative steroid and benzodiazepine are administered sequentially. In some embodiments, neuroative steroid and benzodiazepine are administered in a single dosage form.

When the agents described herein (*e.g.,* the neuroactive steroid and a benzodiazepine) are administered in combination, both of the agents should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a in the absence of the combination regimen. The agents may be administered separately, as part of a

multiple dose regimen. Alternatively, the agents may be part of a single dosage form, mixed together with the compounds of this ~~invention~~ disclosure in a single composition.

In some embodiments, the neuroactive steroid is a progestin derivative, *e.g.*, allopregnanolone. In an embodiment, the neuroactive steroid is allopregnanolone.

In some embodiments, the neruroactive steroid, *e.g.*, alloprenanolone, is formulated for parenteral administration (*e.g.*, intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some embodiments, the neneuroactive steroid, *e.g.*, allopregnanolone, is administered in a composition comprising 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®.

In some embodiments, the cyclodextrin is a β-cyclodextrin. In an embodiment, the cyclodextrin is a sulfo butyl ether β-cyclodextrin. In an embodiment, the cyclodextrin is CAPTISOL®. In some embodiments, the cyclodextrin is a β-cyclodextrin disclosed in U.S. Patent Nos. 5,874,418; 6,046,177; or 7,635,733, which are herein incorporated by reference.

In some embodiments, the neuroactive steroid is a progestin derivative, *e.g.*, allopregnanolone, and the cyclodextrin is a β-cyclodextrin. In an embodiment, the neuroactive steroid is allopregnanolone and the cyclodextrin is CAPTISOL®.

In some embodiments, the neuroactive steroid, *e.g.*, allopregnanolone, and cyclodextrin, *e.g.*, a β-cyclodextrin, *e.g.*, a sulfo butyl ether β-cyclodextrin, *e.g.*, CAPTISOL®, complex is formulated for parenteral administration. In an embodiment, the neuroactive steroid, *e.g.*, allopregnanolone, and cyclodextrin, *e.g.*, a β-cyclodextrin, *e.g.*, a sulfo butyl ether β-cyclodextrin, *e.g.*, CAPTISOL®, complex is formulated as an aqueous composition. In some embodiments, the neuroactive steroid, *e.g.*, allopregnanolone, and cyclodextrin, *e.g.*, a β-cyclodextrin, *e.g.*, a sulfo butyl ether β-cyclodextrin, *e.g.*, CAPTISOL®, complex is formulated as an aqueous composition comprising the neuroactive steroid at a concentration between 0.25-30mg/mL, 0.5-30mg/mL; 1-30mg/mL; 5-30mg/mL, 10-30mg/mL; 15-30mg/mL, 0.25-20mg/mL; 0.5-20mg/mL; 1-20mg/mL, 0.5-20mg/mL; 1-20mg/mL, 5-20mg/mL, 10-20mg/mL, 0.25-15mg/mL, 0.5-15mg/mL; 0.5-10mg/mL; 1-15mg/mL, 1-10mg/mL; 1-5mg/mL; 5-15mg/mL; 5-10mg/mL; 10-15mg/mL; 1-10mg/mL; 2-8mg/mL; 2-7mg/mL; 3-5mg/mL; 5-15mg/mL; 7-12mg/mL; 7-10mg/mL; 8-9mg/mL; 3-5mg/mL; or 3-4mg/mL.

In some embodiments, the benzodiazepine is clonazepam, lorazepam, midazolam, or diazepam.

In some embodiments, the benzodiazepine is formulated for oral delivery. In some embodiments, the benzodiazepine is formulated for parenteral delivery (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some embodiments, both the neuroactive steroid and the benzodiazepine are formulated for parenteral delivery (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly).

In some embodiments, the neuroactive steroid such as allopregnanolone and benzodiazepine, when administered in combination, are administered in an amount sufficient to achieve burst suppression (*e.g.,* a predetermined burst suppression pattern, *e.g.,* inter-burst intervals of between 2-30 seconds; as measured by a method of neurophysiological monitoring, *e.g.,* EEG, CFM). In some embodiments, the neuroactive steroid such as allopregnanolone and benzodiazepine, when administered in combination is administered at a dose sufficient to achieve a predetermined burst suppression pattern, *e.g.,* inter-burst intervals of between 2-30 seconds, 5-30 seconds, 10-30 seconds, 15-30 seconds, 1-30 seconds, 0-30 seconds, 2-20 seconds, 2-10 seconds, 5-20 seconds, 10-20 seconds, 15-25 seconds, 5-15 seconds or 5-10 seconds; as measured by a method of neurophysiological monitoring, *e.g.,* EEG, CFM.

In one ~~aspect~~embodiment, the ~~invention~~ present disclosure features a method of treating a subject (*e.g.,* human subject) having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), comprising: administering to said subject (*e.g.,* human subject), an effective amount of allopregnanolone, wherein, concurrent with said administering, said subject (*e.g.,* human subject) is under general anesthesia, thereby treating said subject (*e.g.,* human subject). In one aspect, the present disclosure features the use of allopregnanolone in the manufacture of a medicament for treating a subject having a seizure-related disorder, e.g., status epilepticus (SE), e.g., refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), wherein the medicament is to be administered to said subject when under general anesthesia, thereby treating said subject.

In one ~~aspect~~embodiment, the ~~invention~~ present disclosure features a method of treating a subject (*e.g.,* human subject) having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), comprising administering a first dose, *e.g.,* a load dose, of allopregnanolone, *e.g.,* to a patient under general anesthesia; administering a second dose, *e.g.,* maintenance dose, of allopregnanolone, which is lower than said first dose; and

administering a third dose, *e.g.*, a downward taper dose, of allopregnanolone, said allopregnanolone doses being sufficient to treat said subject (*e.g.*, human subject). In one aspect, the present disclosure features the use of allopregnanolone for treating a subject having a seizure-related disorder, e.g., status epilepticus (SE), e.g., refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), the medicament comprising: a first dose, e.g., a load dose, of allopregnanolone to be administered, e.g., to a patient under general anesthesia; a second dose, e.g., maintenance dose, of allopregnanolone, which is lower than said first dose, to be administered; and administering a third dose, e.g., a downward taper dose, to be administered, said doses being sufficient to treat said subject.

In some embodiments, said subject (*e.g.*, human subject) is not under general anesthesia for at least a portion of the second dose. In some embodiments, said subject (*e.g.*, human subject) is not under general anesthesia for at least a portion of the third dose. In some embodiments, said subject (*e.g.*, human subject) is under general anesthesia during the administration of the first dose and during administration of a portion of the second dose, *e.g.*, for at least, or up to, 6, 12, 24, or 47 hours of the second dose.

In some embodiments, the second dose is administered over a period of time that is at least 60, 65, 70, 80, 90, 100, 110, 120 times longer in duration than that of said first dose. In some embodiments, the second dose is administered over a period of time that not more than 80, 90, 100, 110, 120, 130, or 140 times longer in duration than that of said first dose.

In some embodiments, the second dose is administered over a period of time that at least 2, 3, 4, 5, 6 times longer in duration than that of said third dose. In some embodiments, the second dose is administered over a period of time that not more than 5, 6, 7, 8, 9, or 10 times longer in duration than that of said third dose.

In some embodiments, the infusion rate, *e.g.*, amount of allopregnanolone delivered/unit time in the second dose, *e.g.*, as measured in μg/kg/hour, is at least 2, 3, 4, 5, or 6 times lower than that of the first dose.

In some embodiments, one, two or all of said doses are injected, *e.g.*, IV administrations.

In some embodiments, said subject (*e.g.*, human subject) has failed to respond to a first line treatment, *e.g.*, a benzodiazepine (*e.g.* midazolam), *e.g.*, as evidenced by a failure to induce an EEG pattern of burst suppression, failure to control seizure, continued seizure activity on EEG recording after 24 hours or more on the first line treatment, or failure to wean from the first line treatment without resuming seizure activity as evidenced by EEG recording.

In some embodiments, said subject (*e.g.*, human subject) has failed to respond to a second line treatment, *e.g.*, phenytoin, fos-phenytoin, valproate, phenobarbitol, or levetiracetam, *e.g.*, as evidenced by a

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 allopregnanolone 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 allopregnanolone.

In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 2.5 mg/mL allopregnanolone. In some embodiments, the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone.

In some embodiments, the method further comprises, evaluating the subject (*e.g.*, human subject), wherein the evaluating comprises performing c-ECG. In some embodiments, the method comprises, evaluating the subject (*e.g.*, human subject), wherein the evaluating comprises performing EEG. In some embodiments, the method further comprises evaluating the subject (*e.g.*, human subject) for serum chemistry (*e.g.*, one or more of albumin, AST, ALT, bicarbonate, bilirubin, BUN, calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, or glucose). In some embodiments, the method further comprises, evaluating the subject (*e.g.*, human subject) for CBC (*e.g.*, one or more of RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, WBC with differential including neutrophils, eosinophils, basophils, lymphocytes, or monocytes. In some embodiments, the method further comprises evaluating the subject (*e.g.*, human subject) for serum allopregnanolone, progesterone, and 5α-dihydrotestosterone. In some embodiments, the method comprises comparing an observed value with a reference value.

In some embodiments, said subject (*e.g.*, human subject) is evaluated for a parameter described herein during said weaning period.

In one ~~aspect~~embodiment, the ~~invention~~ present disclosure features a method of treating a subject (*e.g.*, human subject) having, SE, RSE, or SRSE comprising: administering a first/load, *e.g.*, bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 30-90 minutes; and results in a plasma level of allopregnanolone of 100-

2000 nM allopregnanolone; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 1-60 minutes after the end of the second dose; lasts for 1-6 days; and results in a plasma level of allopregnanolone of 100-2000 nM allopregnanolone; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-100 hours; and results in a plasma level of allopregnanolone of 0-1500 nM allopregnanolone; wherein, collectively, the administrations are provided in sufficient amount to treat said subject (*e.g.*, human subject). In one aspect, the present disclosure features the use of allopregnanolone in the manufacture of a medicament for treating a subject having, status epilepticus (SE), refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), wherein the medicament is to be administered as follows: administering a first/load, *e.g.*, bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 30-90 minutes; and results in a plasma level of allopregnanolone of 100-2000 nM allopregnanolone; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 1-60 minutes after the end of the second dose; lasts for 1-6 days; and results in a plasma level of allopregnanolone of 100-2000 nM allopregnanolone; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-100 hours; and results in a plasma level of allopregnanolone of 0-1500 nM allopregnanolone; wherein, collectively, the administrations are provided in sufficient amount to treat said subject.

In some embodiments, the method comprises administering a first/load, *e.g.*, bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 60 +/-15 minutes; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 70 to 110 hours; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-30 hours.

In some embodiments, administering a first/load, *e.g.*, bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 60 +/-15 minutes; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second

dose; lasts for 70 to 110 hours; and administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 24 +/- 2 hours and said third downward taper dose comprises a first, second, and third step dose.

In some embodiments, administering a first/load, *e.g.*, bolus, dose concurrent with general anesthesia, wherein administration of said first dose lasts for 60 +/-15 minutes; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 85 to 105 hours; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-30 hours and: the amount of allopregnanolone delivered/unit time in said first step dose is 70 to 80% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; the amount of allopregnanolone delivered/unit time in said second step dose is 40 to 60% of the amount of allopregnanolone delivered/unit time in

said second/maintenance dose; and the amount of allopregnanolone delivered/unit time in said third step dose is 20 to 30% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

In some embodiments, administering a first/load, *e.g.*, bolus, dose concurrent with general anesthesia, wherein administration of said first dose lasts for 60 +/-5 minutes; administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 96+/-4 hours; administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 24+/-2 hours and: the amount of allopregnanolone delivered/unit time in said first step dose is 75% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; the amount of allopregnanolone delivered/unit time in said second step dose is 50% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; and the amount of allopregnanolone delivered/unit time in said third step dose is 25% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

In some embodiments, the method further comprises administering an amount of a composition selected from benzodiazepines (*e.g.*, midazolam), propofol, barbiturates, and ketamine sufficient to place said subject (*e.g.*, human subject) under general anesthesia;

In one aspect, the ~~invention~~ present disclosure features a kit comprising one or more of: a preparation of allopregnanolone, *e.g.*, a plurality of preparations of allopregnanolone at a concentrations suitable for use at the first, second, and third doses; and instructions for use for treating a subject (*e.g.*, human subject) having a seizure-related disorder, *e.g.*, status epilepticus (SE), *e.g.*, super-refractory status epilepticus (SRSE).

In some embodiments, the kit further comprises a suitable diluent (*e.g.*, water, saline, cyclodextrin, *e.g.*, β-cyclodextrin, *e.g.*, sulfo butyl ether β-cyclodextrin, *e.g.*, CAPTISOL).

In some embodiments, the allopregnanolone is provided at a concentration of 0.1-10 mg/mL allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 0.5-7.5 mg/mL allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 1-6 mg/mL allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone. In some

embodiments, the allopregnanolone is provided at a concentration of 2.5 allopregnanolone. In some embodiments, the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone.

In one aspect, the ~~invention~~ present disclosure features a method of making a series of dosages, the method comprising combining a diluent and allopregnanolone in proportions to ~~from~~ form dosage forms suitable for use as the first, second and one or more step doses for said third dose.

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

In one ~~aspect~~embodiment, the ~~invention~~ present disclosure features a method of treating a subject having seizure, epilepsy or status epilepticus by administering in combination to the subject a neuroactive steroid and a benzodiazepine or anesthetic/sedative. In some embodiments, the method further comprises administering at least one of the neuroactive steroid and benzodiazepine or anesthetic/sedative parenterally (*e.g.,* intranasally, buccally, intravenously or intramuscularly, for example, intravenously or intramuscularly). In some embodiments, both the neuroactive steroid and benzodiazepine or anesthetic/sedative are administered parenterally.

In some embodiments, the neuroactive steroid and benzodiazepine or anesthetic/sedative co-administered (*e.g.,* administered simultaneously, administered concurrently). In some embodiments, the neuroactive steroid and benzodiazepine or anesthetic/sedative are administered sequentially. In some embodiments, neuroactive steroid and benzodiazepine or anesthetic/sedative are administered in a single dosage form.

When the agents described herein (*e.g.,* the neuroactive steroid and a benzodiazepine or anesthetic/sedative) are administered in combination, both of the agents should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in the absence of the combination regimen. The agents may be administered separately, as part of a multiple dose regimen. Alternatively, the agents may be part of a single dosage form, mixed together with the compounds of this ~~invention~~ disclosure in a single composition.

We claim:

1. ~~A method of~~ Use of allopregnanolone in the manufacture of a medicament for treating a subject having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), ~~the method comprising:~~

~~administering to said subject, an effective amount of allopregnanolone,~~

~~wherein~~ the medicament is to be~~,~~ administered to ~~concurrent with said administering,~~ said subject ~~is~~ when under general anesthesia,

thereby treating said subject.

2. ~~A method of~~ Use of allopregnanolone in the manufacture of a medicament for treating a subject having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), ~~the method comprising~~wherein the medicament is to be administered as follows:

administering a first dose, *e.g.,* a load dose, of allopregnanolone, *e.g.,* administered to a patient under general anesthesia;

administering a second dose, *e.g.,* maintenance dose, of allopregnanolone, which is lower than said first dose; and

administering a third dose, *e.g.,* a downward taper dose, of allopregnanolone,

said allopregnanolone doses being sufficient to treat said subject.

3. The ~~method~~ use of claim 2, wherein said subject is not under general anesthesia for: at least a portion of the second dose; at least a portion of the third dose.

4. The ~~method~~ use of claim 2, wherein said subject is under general anesthesia during the administration of the first dose and during administration of a portion of the second dose, *e.g.,* for at least, or up to, 6, 12, 24, or 47 hours of the second dose.

5. The use ~~method~~ of claim 2, wherein the second dose is to be administered over a period of time that is at least 60, 65, 70, 80, 90, 100, 110, or 120 times longer in duration than that of said first dose.

6. The use ~~method~~ of claim 2, wherein the second dose is to be administered over a period of time that not more than 80, 90, 100, 110, 120, 130, or 140 times longer in duration than that of said first dose.

7. The use ~~method~~ of claim 2, wherein the second dose is to be administered over a period of time that is at least 2, 3, 4, 5, 6 times longer in duration than that of said third dose.

8. The use ~~method~~ of claim 2, wherein the second dose is to be administered over a period of time that is not more than 5, 6, 7, 8, 9, or 10 times longer in duration than that of said third dose.

9. The use ~~method~~ of claim 2, wherein the amount of allopregnanolone delivered/unit time in the second dose, *e.g.,* as measured in μg/kg/hour, is at least 2, 3, 4, 5, or 6 times lower than that of the first dose.

10. The use ~~method~~ of claim 2, wherein one, two or all of said doses are to be injected, *e.g.,* IV administrations.

11. The use ~~method~~ of claim 2, wherein said subject has failed to respond to a first line treatment, *e.g.,* benzodiazepine, *e.g.,* as evidenced by a failure to induce an EEG pattern of burst suppression, failure to control seizure, continued seizure activity on EEG recording after 24 hours or more on the first line treatment, or failure to wean from the first line treatment without resuming seizure activity as evidenced by EEG recording.

12. The use ~~method~~ of claim 2, wherein said subject has failed to respond to a second line treatment, *e.g.,* phenytoin, fos-phenytoin, valproate, phenobarbitol, or levetiracetam, *e.g.,* as evidenced by a failure to induce an EEG pattern of burst suppression, failure to control seizure, continued seizure activity on EEG recording after 24 hours or more on the first line treatment, or failure to wean from the first line treatment without resuming seizure activity as evidenced by EEG recording.

13. The use ~~method~~ of claim 2, further comprising administering an amount of an anesthetic effective to place said subject under general anesthesia.

14. The use ~~method~~ of claim 2, wherein said anesthetic is selected from benzodiazepine (*e.g.*, midazolam), propofol, pentobarbital, and ketamine.

15. The use ~~method~~ of claim 2, further comprising a weaning period in which said subject is weaned from said general anesthesia.

16. The use ~~method~~ of claim 15, wherein said weaning period is initiated during the administration of said second dose.

17. The use ~~method~~ of claim 15, wherein said weaning period is completed during the administration of said second dose.

18. The use ~~method~~ of claim 15, in which said weaning period is initiated within 12, 24, 36, 48, 60 or 72 hours after initiation or completion of the first dose of allopregnanolone.

19. The use ~~method~~ of claim 15, in which said weaning period is initiated at 48 hours after initiation or completion of the first dose of allopregnanolone.

20. The use ~~method~~ of claim 15, wherein said weaning period is 18 to 30 hours, 20 to 28 hours, or 22 to 26 hours in duration.

21. The use ~~method~~ of claim 15, wherein said weaning period is 24 hours in duration.

22. The use ~~method~~ of claim 1, wherein the administration of allopregnanolone, *e.g.*, the first or load dose, is initiated within a preselected period of time, wherein said period begins with: the administration of said anesthetic; or the induction of general anesthesia.

23. The use ~~method~~ of claim 22, wherein said preselected period is not longer than 48, 24, 12, 6, 5, 4, 3, 2, or 1 hour.

24. The use ~~method~~ of claim 22, wherein said preselected period is not longer than 120, 60, 30, 15, or 5 minutes.

25. The use ~~method~~ of claim 2, wherein said second dose is initiated while the subject is under general anesthesia.

26. The use ~~method~~ of claim 2, wherein the amount of allopregnanolone delivered per hour in said second dose is the same or lower than the amount delivered per hour in said first dose.

27. The use ~~method~~ of claim 2, wherein the administration of the first dose of allopregnanolone is initiated within a preselected period of time, wherein said period begins with: the administration of said anesthetic; or the induction of general anesthesia.

28. The use ~~method~~ of claim 27, wherein said preselected period is at least 6, 12, 24, 48 or 60 hours.

29. The use ~~method~~ of claim 27, wherein said preselected period is not longer than 24, 48, or 60 hours.

30. The use ~~method~~ of claim 27, wherein said preselected period is between 2 to 120, 2 to 60, 4 to 120, 4 to 60, 4 to 48, 4 to 36, or 4 to 24 hours.

31. The use ~~method~~ of claim 27, wherein said preselected period is not longer than 48, 24, 12, 6, 5, 4, 3, 2, or 1 hour.

32. The use ~~method~~ of claim 27, wherein said preselected period is not longer than 120, 60, 30, 15, or 5 minutes.

33. The use ~~method~~ of claim 2, wherein said first dose is begun after failure of the subject to respond to prior treatment.

34. The use ~~method~~ of claim 33, wherein failure to respond is evidenced by one or more of, a failure to induce an EEG pattern of burst suppression, failure to control seizure, continued seizure activity on EEG recording after 24 hours or more on the first line treatment, or failure to wean from the first line treatment without resuming seizure activity as evidenced by EEG recording.

35. The use ~~method~~ of claim 33, wherein said prior treatment comprises administration of a first line treatment, *e.g.,* benzodiazepine.

36. The use ~~method~~ of claim 33, wherein said prior treatment comprises administration of a second line treatment, *e.g.,* phenytoin, fos-phenytoin, valproate, phenobarbitol, or levetiracetam.

37. The use ~~method~~ of claim 2, said first dose is a load, *e.g.,* bolus, dose.

38. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 50 to 500 nM, 100 to 400 nM, or 200 to 300 nM.

39. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 500 to 1000 nM, 600 to 900 nM, or 700 to 800 nM.

40. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 1000 to 1500 nM, 1100 to 1400 nM, or 1200 to 1300 nM.

41. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 1500 to 2000 nM, 1600 to 1900 nM, or 1700 to 1800 nM.

42. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 2000 to 2500 nM, 2100 to 2400 nM, or 2200 to 2300 nM.

43. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 300 to 800 nM, 400 to 700 nM, or 500 to 600 nM.

44. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 800 to 1300 nM, 900 to 1200 nM, or 1000 to 1100 nM.

45. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 1300 to 1800 nM, 1400 to 1700 nM, or 1500 to 1600 nM.

46. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 1800 to 2300 nM, 1900 to 2200 nM, or 2000 to 2100 nM.

47. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 2300 to 2600 nM, 2400 to 2500 nM.

48. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 300 to 400 nM, 400 to 500, 600 to 700, 800 to 900, 1100 to 1200, 1300 to 1400, 1400 to 1500, 1600 to 1700, 1800 to 1900, 1900 to 2000, 2100 to 2200, 2300 to 2400 nM.

49. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 500 to 2500 nM, 500 to 1500 nM, 500 to 1000 nM, 500 to 800, or 500 to 600, nM.

50. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 50 to 250 nM, 100 to 200 nM, or 140 to 160 nM.

51. The use ~~method~~ of claim 37, wherein said load dose results in a plasma concentration of 150 +/- 30 nM, 150 +/- 20 nM, 150 +/- 10 nM, or 150 nM.

52. The use ~~method~~ of claim 2, wherein the plasma concentration of said first 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 first dose.

53. The use ~~method~~ of claim 2, said first dose is to be administered over a period of time that is not longer than 6, 5, 4, 3, 2, or 1 hour.

54. The use ~~method~~ of claim 2, said first dose is to be administered over a period of time that is at least 10, 20, 30, 40, 50, 60, 70, 80, or 90 minutes in duration.

55. The use ~~method~~ of claim 2, said first dose is to be administered over a period of time that is 30 to 120 minutes, 45 to 100 minutes, or 50 to 70 minutes, in duration.

56. The use ~~method~~ of claim 2, said first dose is to be administered over a period of time that is 60 +/- 15 minutes, 60 +/- 10 minutes, 60 +/- 5 minutes, or 60 minutes, in duration.

57. The use ~~method~~ of claim 2, said first dose is to be administered at a dosage rate of 200-3500 μg/kg/hour.

58. The use ~~method~~ of claim 2, said first dose is to be administered at a dosage rate of 200-350 μg/kg/hour, 250-300 μg/kg/hour, 280-290 μg/kg/hour, 286 μg/kg/hour, 287 μg/kg/hour, or 288 μg/kg/hour, *e.g.*, for one hour.

59. The use ~~method~~ of claim 2, said second dose is a maintenance dose.

60. The use ~~method~~ of claim 2, wherein the administration said second dose is initiated within a preselected time period, wherein said time period begins with: the administration of said anesthetic; the induction of general anesthesia; the beginning of the first dose; the end of the first dose; the achievement of a predetermined level of allopregnanolone, *e.g.*, in the plasma.

61. The use ~~method~~ of claim 60, wherein said time period begins with the end of the first dose.

62. The use ~~method~~ of claim 2, wherein said preselected time period begins with beginning or ending of the administration of the first dose and is not longer than 240, 180, 120, 60, 30, 15, or 5 minutes.

63. The use ~~method~~ of claim 2, wherein said preselected time period begins with beginning or ending of the administration of the first dose and is not longer than 90, 80, 70, or 60 minutes.

64. The use ~~method~~ of claim 2, wherein the administration of the second dose begins no longer than 90, 80, 70, 60, or 30 minutes after the beginning or end of the administration of the first dose.

65. The use ~~method~~ of claim 2, wherein the second dose begins 50 to 70, 55 to 65, or 60 minutes after the beginning or end of the administration of the first dose.

66. The use ~~method~~ of claim 2, wherein the second dose begins no more than 60, 50, 40, 30, 20, 10, 5, 4, 3, 2, 1 minute after the end of administration of the first dose.

67. The use ~~method~~ of claim 2, wherein the second dose begins at the end of administration of the first dose.

68. The use ~~method~~ of claim 2, wherein 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.

69. The use ~~method~~ of claim 2, wherein said second dose is to be administered for a period of time that is between 48 and 192 hours, 60 and 144 hours, 60 and 120 hours, 80 and 110 hours, or 90 and 100 hours.

70. The use ~~method~~ of claim 2, wherein said second dose is to be administered for 95+/-5 hours.

71. The use ~~method~~ of claim 2, wherein said second dose is to be administered for 95 hours.

72. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 50 to 500 nM, 100 to 400 nM, or 200 to 300 nM.

73. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 500 to 1000 nM, 600 to 900 nM, or 700 to 800 nM.

74. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 1000 to 1500 nM, 1100 to 1400 nM, or 1200 to 1300 nM.

75. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 1500 to 2000 nM, 1600 to 1900 nM, or 1700 to 1800 nM.

76. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 2000 to 2500 nM, 2100 to 2400 nM, or 2200 to 2300 nM.

77. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 300 to 800 nM, 400 to 700 nM, or 500 to 600 nM.

78. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 800 to 1300 nM, 900 to 1200 nM, or 1000 to 1100 nM.

79. The use ~~method~~ of claim 2, wherein said first dose results in a plasma concentration of 1300 to 1800 nM, 1400 to 1700 nM, or 1500 to 1600 nM.

80. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 1800 to 2300 nM, 1900 to 2200 nM, or 2000 to 2100 nM.

81. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 2300 to 2600 nM, 2400 to 2500 nM.

82. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 300 to 400 nM, 400 to 500, 600 to 700, 800 to 900, 1100 to 1200, 1300 to 1400, 1400 to 1500, 1600 to 1700, 1800 to 1900, 1900 to 2000, 2100 to 2200, 2300 to 2400 nM.

83. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 500 to 2500 nM, 500 to 1500 nM, 500 to 1000 nM, 500 to 800, or 500 to 600, nM.

84. The use ~~method~~ of claim 2, wherein said second dose results in a plasma concentration of 50 to 250 nM, 100 to 200 nM, or 140 to 160 nM.

85. The use ~~method~~ of claim 37, wherein said second dose results in a plasma concentration of 150 +/- 30 nM, 150 +/- 20 nM, 150 +/- 10 nM, or 150 nM

86. The use ~~method~~ of claim 2, wherein the plasma concentration of said second 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 second dose.

87. The ~~method~~use of claim 2, wherein said second 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 second dose.

88. The ~~method~~use of claim 2, wherein said second dose is to be administered at the same amount of allopregnanolone /unit time over the entire second dose.

89. The ~~method~~use of claim 2, wherein the amount of allopregnanolone delivered/unit time varies during the second dose.

90. The ~~method~~use of claim 2, said second dose is to be administered at an amount of allopregnanolone/unit time of 25-1500 μg/kg/hour.

91. The ~~method~~use of claim 2, said second dose is to be administered at an amount of allopregnanolone/unit time of 25-150 μg/kg/hour, 50-100 μg/kg/hour, 75-100 μg/kg/hour, 85 μg/kg/hour, 86 μg/kg/hour, or 87 μg/kg/hour.

92. The ~~method~~use of claim 2, wherein administering said downward taper dose comprises administering a continuously decreasing amount of allopregnanolone.

93. The ~~method~~use of claim 2, wherein administering said downward taper dose comprises administering a continuously decreasing amount of allopregnanolone/unit time.

94. The ~~method~~use of claim 2, wherein said downward taper dose comprises administering a plurality of step doses, wherein each subsequent step dose is lower than the step dose that precedes it.

95. The ~~method~~use of claim 2, wherein administering said downward taper dose comprises administering a plurality of step doses, wherein each subsequent step dose delivers a lower amount of allopregnanolone/unit time than the step dose that precedes it.

96. The ~~method~~use of claim 95, comprising administering a first, second, and third step dose.

97. The ~~method~~use of claim 96, wherein:

said first step dose is 60 to 90% of the second/maintenance dose;

said second step dose is 40 to 70% of the second/maintenance dose; and

said third step dose is 10 to 40% of the second/maintenance dose.

98. The ~~method~~use of claim 96, wherein:

the amount of allopregnanolone delivered/unit time in said first step dose is 60 to 90% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose;

the amount of allopregnanolone delivered/unit time in said second step dose is 40 to 70% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; and

the amount of allopregnanolone delivered/unit time in said third step dose is 10 to 40% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

99. The ~~method~~use of claim 96, wherein:

said first step dose is 70 to 80% of the second/maintenance dose;

said second step dose is 40 to 60% of the second/maintenance dose; and

said third step dose is 20 to 30% of the second/maintenance dose.

100. The ~~method~~use of claim 96, wherein:

the amount of allopregnanolone delivered/unit time in said first step dose is 70 to 80% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose;

the amount of allopregnanolone delivered/unit time in said second step dose is 40 to 60% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; and

the amount of allopregnanolone delivered/unit time in said third step dose is 20 to 30% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

101. The ~~method~~use of claim 96, wherein:

said first step dose is 75% of the second/maintenance dose;

said second step dose is 50% of the second/maintenance dose; and

said third step dose is 25% of the second/maintenance dose.

102. The ~~method~~use of claim 96, wherein:

the amount of allopregnanolone delivered/unit time in said first step dose is 75% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose;

the amount of allopregnanolone delivered/unit time in said second step dose is 50% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose; and

the amount of allopregnanolone delivered/unit time in said third step dose is 25% of the amount of allopregnanolone delivered/unit time in said second/maintenance dose.

103. The ~~method~~use of claim 96, wherein, after the completion of said third step dose, no allopregnanolone is to be administered to the subject for at least 10, 20, 30, 40, 50, or 60 days, or until the patient has a subsequent episode of SRSE.

104. The ~~method~~use of claim 96, said first step dose is to be administered at an amount of allopregnanolone/unit time of 25-1000 μg/kg/hour.

105. The ~~method~~use of claim 96, said first step dose is to be administered at an amount of allopregnanolone/unit time of 25-100 μg/kg/hour, 50-75 μg/kg/hour, 60-70 μg/kg/hour, 63 μg/kg/hour, 64 μg/kg/hour, or 65 μg/kg/hour.

106. The ~~method~~use of claim 96, said second step dose is to be administered at an amount of allopregnanolone/unit time of 10-700 μg/kg/hour.

107. The ~~method~~use of claim 96, said second step dose is to be administered at an amount of allopregnanolone/unit time of 10-70 μg/kg/hour, 25-55 μg/kg/hour, 40-50 μg/kg/hour, 42 μg/kg/hour, 43 μg/kg/hour, or 44 μg/kg/hour.

108. The ~~method~~use of claim 96, said third step dose is to be administered at an amount of allopregnanolone/unit time of 5-500 μg/kg/hour,

109. The ~~method~~use of claim 96, said third step dose is to be administered at an amount of allopregnanolone/unit time of 5-50 μg/kg/hour, 10-35 μg/kg/hour, 15-25 μg/kg/hour, 20 μg/kg/hour, 21 μg/kg/hour, or 22 μg/kg/hour.

110. The ~~method~~use of claim 96, wherein the administration of the third/taper dose begins no longer than 90, 80, 70, 60, or 30 minutes after the administration or end of the second dose.

111. The ~~method~~use of claim 96, wherein the administration of the third/taper dose begins at the end of administration of the second dose.

112. The ~~method~~use of claim 96, wherein the administration of the second dose and the initiation of third/taper dose are performed with the same delivery device, *e.g.*, the same cannula.

113. The ~~method~~use of claim 96, wherein the time between the end of the administration of said first step dose and the initiation of administration of said second step dose is less than 120, 60, 30, 15 or 5 minutes.

114. The ~~method~~use of claim 96, wherein the time between the end of the administration of said second step dose and the initiation of administration of said third step dose is less than 120, 60, 30, 15 or 5 minutes.

115. The ~~method~~use of claim 96, wherein said third dose is to be administered for a period of time that is between 10 and 100 hours, 12 and 96 hours, 12 and 48 hours, 16 and 32 hours, or 20 and 30 hours.

116. The ~~method~~use of claim 2, wherein said third dose is to be administered over 24 hours.

117. The ~~method~~use of claim 2, wherein the allopregnanolone is provided in a composition comprising a cyclodextrin, *e.g.*, β-cyclodextrin, *e.g.*, sulfo butyl ether β-cyclodextrin, *e.g.*, CAPTISOL.

118. The ~~method~~use of claim 2, wherein the allopregnanolone is provided at a concentration of 0.1 to 10 mg/mL allopregnanolone.

119. The ~~method~~use of claim 2, wherein the allopregnanolone 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 allopregnanolone.

120. The ~~method~~use of claim 2, wherein the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone.

121. The ~~method~~use of claim 2, wherein the allopregnanolone is provided at a concentration of 2.5 mg/mL allopregnanolone.

122. The ~~method~~use of claim 2, wherein the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone.

123. The ~~method~~use of claim 2, wherein the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone.

124. The ~~method~~use of claim 117, wherein the cyclodextrin is present in the composition at 1-30%, 2-18%, 10-15% by weight of cyclodextrin per volume of composition.

125. The ~~method~~use of claim 117, wherein 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.

126. The ~~method~~use of claim 117, wherein the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition.

127. The ~~method~~use of claim 117, wherein the cyclodextrin is present in the composition at 1-30%, 2-18%, 10-15% by weight of cyclodextrin per volume of composition and the allopregnanolone 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 allopregnanolone.

128. The ~~method~~use of claim 117, wherein 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 allopregnanolone 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 allopregnanolone.

129. The ~~method~~use of claim 117, wherein the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone.

130. The ~~method~~use of claim 117, wherein the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone.

131. The ~~method~~use of claim 117, wherein the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 2.5 mg/mL allopregnanolone.

132. The ~~method~~use of claim 117, wherein the cyclodextrin is present in the composition at 12% by weight of cyclodextrin per volume of composition and the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone.

133. The ~~method~~use of claim 1, ~~further comprising, evaluating~~wherein the subject is to be evaluated, wherein the evaluating comprises performing c-ECG.

134. The ~~method~~use of claim 1, ~~further comprising evaluating~~wherein the subject is to be evaluated, wherein the evaluating comprises performing EEG.

135. The ~~method~~use of claim 1, ~~further comprising, evaluating~~wherein the subject is to be evaluated for serum chemistry (*e.g.,* one or more of albumin, AST, ALT, bicarbonate, bilirubin, BUN, calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, or glucose).

136. The ~~method~~use of claim 1, ~~further comprising, evaluating~~wherein the subject is to be evaluated for CBC (*e.g.,* one or more of RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, WBC with differential including neutrophils, eosinophils, basophils, lymphocytes, or monocytes.

137. The ~~method~~use of claim 1, ~~further comprising, evaluating~~wherein the subject is to be evaluated for serum allopregnanolone, progesterone, and 5α-dihydrotestosterone.

138. The ~~method~~use of any of claims 133-137, comprising comparing an observed value with a reference value.

139. The ~~method~~use of any of claims 133-137, wherein said subject is to be evaluated for a parameter described herein during said weaning period.

140. ~~A method of~~ Use of allopregnanolone in the manufacture of a medicament for treating a subject having, status epilepticus (SE), refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE), wherein the medicament is to be administered as follows~~comprising~~:

administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 30-90 minutes; and results in a plasma level of allopregnanolone of 100-2000 nM allopregnanolone;

administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 1-60 minutes after the end of the second dose; lasts for 1-6 days; and results in a plasma level of allopregnanolone of 100-2000 nM allopregnanolone;

administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-100 hours; and results in a plasma level of allopregnanolone of 0-1500 nM allopregnanolone;

wherein, collectively, the administrations are provided in sufficient amount to treat said subject.

141. The ~~method~~ use of claim 140, wherein:

administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 60 +/-15 minutes;

administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 70 to 110 hours;

administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-30 hours.

142. The ~~method~~ use of claim 140, wherein:

administering a first/load, *e.g.*, bolus, dose concurrent with general anesthesia, wherein administration of said first dose: begins 2-120 hours after induction of general anesthesia; lasts for 60 +/- 15 minutes;

administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 70 to 110 hours; and

administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 24 +/- 2 hours and said third downward taper dose comprises a first, second, and third step dose.

143. The ~~method~~ use of claim 142, wherein:

administering a first/load, *e.g.*, bolus, dose concurrent with general anesthesia, wherein administration of said first dose lasts for 60 +/-15 minutes;

administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 85 to 105 hours;

administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 10-30 hours and:

the amount of ~~allopregnanolone~~ medicament delivered/unit time in said first step dose is 70 to 80% of the amount of medicament ~~allopregnanolone~~ delivered/unit time in said second/maintenance dose;

the amount of medicament ~~allopregnanolone~~ delivered/unit time in said second step dose is 40 to 60% of the amount of medicament ~~allopregnanolone~~ delivered/unit time in said second/maintenance dose; and

the amount of medicament ~~allopregnanolone~~ delivered/unit time in said third step dose is 20 to 30% of the amount of medicament ~~allopregnanolone~~ delivered/unit time in said second/maintenance dose.

144. The use ~~method~~ of claim 143, wherein:

administering a first/load, *e.g.,* bolus, dose concurrent with general anesthesia, wherein administration of said first dose lasts for 60 +/-5 minutes;

administering a second/maintenance dose, wherein, the administration of said second dose begins not longer than 30 minutes after the end of the second dose; lasts for 96+/-4 hours;

administering a third downward taper dose, wherein, the administration of said third downward taper dose begins not longer than 1-60 minutes after the end of the third dose; lasts for 24+/-2 hours and:

the amount of medicament ~~allopregnanolone~~ delivered/unit time in said first step dose is 75% of the amount of medicament ~~allopregnanolone~~ delivered/unit time in said second/maintenance dose;

the amount of medicament ~~allopregnanolone~~ delivered/unit time in said second step dose is 50% of the amount of medicament ~~allopregnanolone~~ delivered/unit time in said second/maintenance dose; and

the amount of medicament ~~allopregnanolone~~ delivered/unit time in said third step dose is 25% of the amount of medicament ~~allopregnanolone~~ delivered/unit time in said second/maintenance dose.

145. The ~~method~~use of claim 140, further comprising,

administering an amount of a composition selected from benzodiazepines, propofol, and barbiturates, sufficient to place said subject under general anesthesia.~~;~~

146. A kit comprising one or more of: a preparation of allopregnanolone, *e.g.,* a plurality of preparations of allopregnanolone at concentrations suitable for use at the first, second, and third dosages; and instructions for use for treating a subject having a seizure-related disorder, *e.g.,* status epilepticus (SE), *e.g.,* super-refractory status epilepticus (SRSE).

147. The kit of claim 146, further comprising a suitable diluent (*e.g.,* water, saline, cyclodextrin, *e.g.,* β-cyclodextrin, *e.g.,* sulfo butyl ether β-cyclodextrin, *e.g.,* CAPTISOL).

148. The kit of claim 146, wherein the allopregnanolone is provided at a concentration of 0.1-10 mg/mL allopregnanolone.

149. The kit of claim 148, wherein the allopregnanolone is provided at a concentration of 0.5-7.5 mg/mL allopregnanolone.

150. The kit of claim 149, wherein the allopregnanolone is provided at a concentration of 1-6 mg/mL allopregnanolone.

151. The kit of claim 150, wherein the allopregnanolone is provided at a concentration of 5 mg/mL allopregnanolone.

152. The kit of claim 150, wherein the allopregnanolone is provided at a concentration of 3.75 mg/mL allopregnanolone.

153. The kit of claim 150, wherein the allopregnanolone is provided at a concentration of 2.5 allopregnanolone.

154. The kit of claim 150, wherein the allopregnanolone is provided at a concentration of 1.25 mg/mL allopregnanolone.

155. A method of making a series of dosages, the method comprising combining a diluent and allopregnanolone in proportions to ~~from~~ form dosage forms suitable for use as the first, second and one or more step doses for said third dose.

156. A method of adjusting the amount of diluents and /or allopregnanolone flowing into or out of a delivery device, *e.g.,* a catheter, reservoir, the method comprising altering, *e.g.,* decreasing, the flow rate of allopregnanolone 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.

157. The use ~~method~~ of claim 2, wherein the administration of said first dose is initiated while said subject is under general anesthesia.

158. The use ~~method~~ of claim 2, wherein the administration of said first dose is initiated prior to said subject undergoing general anesthesia.

159. The use ~~method~~ of claim 2, wherein the administration of the first dose is initiated prior to the initiation of the administration of an anesthetic.

160. The use ~~method~~ of claim 2, wherein the administration of the first dose is initiated after the initiation of the administration of an anesthetic.

161. The use ~~method~~ of claim 2, wherein the administration of the first dose, and the administration of an anesthetic, are initiated at the same time.

162. The use ~~method~~ of claim 2, wherein the administration of the first dose, and the administration of an anesthetic, are initiated within, 5, 10, 60, 120, 180, 240, or 300 minutes of one another.

163. The use ~~method~~ of claim 162, wherein the administration of the first dose is initiated prior to the initiation of administration of an anesthetic.

164. The use ~~method~~ of claim 162, wherein the administration of the first dose is initiated after the initiation of administration of an anesthetic.