epilepticus, non-convulsive status epilepticus, the methods comprising administering to the subject a composition described herein, e.g., a neuroactive steroid, e.g., allopregnanolone, and optionally a cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., CAPTISOL®..

In one aspect, there is provided use of an effective amount of a dosage formulation of allopregnanolone in a cyclodextrin carrier in the manufacture of a medicament for treating a traumatic brain injury in an individual in need thereof for treatment of a central nervous system injury.

In one aspect, there is provided a pharmaceutical dosage unit comprising complex of an allopregnanolone and a cyclodextrin.

In one aspect, there is provided use of an effective amount of a dosage formulation of allopregnanolone in a cyclodextrin carrier in the manufacture of a medicament for treating a CNS disorder in a subject.

In one aspect, there is provided use of an effective amount of a dosage formulation of allopregnanolone in the manufacture of a medicament for treating a CNS disorder in a subject, wherein the CNS disorder is a seizure or status epilepticus.

In one embodiment, the disclosure features a composition, the composition comprising a neuroactive steroid, e.g., allopregnanolone, and cyclodextrin, e.g., a neuroactive steroid, e.g., allopregnanolone, 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., allopregnanolone. In an embodiment, the neuroactive steroid is allopregnanolone.

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.,

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 comprising the neuroactive steroid, e.g., allopregnanolone, at a concentration of 1.5mg/mL, and the cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., CAPTISOL®, at a concentration of 30%. 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 comprising the neuroactive steroid, e.g., allopregnanolone, at a concentration of 10mg/mL, and the cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., CAPTISOL®, at a concentration of 30%. 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 comprising the neuroactive steroid, e.g., allopregnanolone, at a concentration of 15mg/mL, and the cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., CAPTISOL®, at a concentration of 30%.

In some embodiments, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH between 3-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-9, 5-8, 5-7, 5-6, 4.5-7.5, or 5.5-7.5. In some embodiments, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH about 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, or 9. In an embodiment, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH about 6.

In one embodiment, the disclosure features a composition, the composition comprising a neuroactive steroid, e.g., allopregnanolone, and cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., a β-cyclodextrin,

the cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., CAPTISOL®, at a concentration of 30%. 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 comprising the neuroactive steroid, e.g., allopregnanolone, at a concentration of 10mg/mL, and the cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., CAPTISOL®, at a concentration of 30%. 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 comprising the neuroactive steroid, e.g., allopregnanolone, at a concentration of 15mg/mL, and the cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., CAPTISOL®, at a concentration of 30%.

In some embodiments, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH between 3-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-9, 5-8, 5-7, 5-6, 4.5-7.5, or 5.5-7.5. In some embodiments, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH about 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, or 9. In an embodiment, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition with a pH about 6.

In one embodiment, the disclosure features a method of treating a subject having a CNS disorder, e.g., a traumatic brain injury, 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 some embodiments, the neuroactive steroid is a progestin derivative, e.g., allopregnanolone. In an embodiment, the neuroactive steroid is allopregnanolone.

In some embodiments, the CNS disorder is a traumatic brain injury. In some embodiments, the CNS disorder is status epilepticus, 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. In some embodiments, the CNS disorder is a traumatic brain injury. In some embodiments, the CNS disorder is a seizure, e.g., acute repetitive seizures, cluster seizures.

In an embodiment, the disclosure features a method of treating a subject having status epilepticus, e.g., refractory convulsive status epilepticus, non-convulsive status epilepticus, the method comprising administering to the subject allopregnanolone. In an embodiment, the disclosure features a method of treating a subject having a traumatic brain injury the method comprising administering to the subject allopregnanolone.

In one embodiment, the disclosure features a method of treating a subject having a CNS disorder, e.g., a traumatic brain injury, 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, e.g., allopregnanolone, and cyclodextrin, e.g., a β-

formulated as an aqueous composition and is administered within 8 hours after a traumatic brain injury.

In some embodiments, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered within 10 hours, 8 hours, 5 hours, 3 hours, 1 hour, or 0.5 hour after a seizure, e.g., a status epileptic seizure, e.g., a refractory status epileptic seizure has started. In some embodiments, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered within 60 minutes, 45 minutes, 30 minutes, 15 minutes, 10 minutes, or 5 minutes after a seizure, e.g., a status epileptic seizure, e.g., a refractory status epileptic seizure has started. In some embodiments, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered after a seizure, e.g., a status epileptic seizure, e.g., a refractory status epileptic seizure has lasted 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes or 60 minutes.

In some embodiments, the allopregnanolone and CAPTISOL® complex is formulated as an aqueous composition and is administered prior to the onset of a seizure, e.g., a status epileptic seizure, e.g., a refractory status epileptic seizure.

In one embodiment, the disclosure features a method of treating a subject having a CNS disorder, e.g., a traumatic brain injury, 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, e.g., allopregnanolone, and cyclodextrin, e.g., a β-cyclodextrin, e.g., a sulfo butyl ether β-cyclodextrin, e.g., a β-cyclodextrin, e.g.,

We claim:

1. Use of an effective amount of a dosage formulation of allopregnanolone in a cyclodextrin carrier in the manufacture of a medicament for treating a traumatic brain injury in an individual in need thereof for treatment of a central nervous system injury.

2. The use of claim 1, wherein the allopregnanolone is to be administered in a therapeutically effective two-level dosing regimen of allopregnanolone, including a first time period, wherein a first hourly dose of allopregnanolone is to be administered to the subject, followed by a second time period, wherein a lower hourly infusion dose of allopregnanolone is to be administered.

3. The use of claim 2, wherein the allopregnanolone is to be administered a loading dose administered over 1 hour followed by a maintenance infusion for the next 95 hours, and then tapered off by reducing the dose.

4. The use of claim 1, wherein the allopregnanolone is to be administered over a period of five days.

5. The use of claim 1, wherein the concentration of the allopregnanolone is between about 0.25mg/mLand about 15mg/mL.

6. The use of claim 1, wherein the concentration of the allopregnanolone is about 1.5mg/mL.

7. The use of claim 1, wherein the dosage of allopregnanolone administered by infusion produces a steady-state serum allopregnanolone concentration between about 150 nM and 2500 nM.

8. The use of claim 1, wherein the allopregnanolone (3α,5α-tetrahydroprogesterone), is formulated with 6% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

9. The use of claim 1, wherein the allopregnanolone (3α,5α-tetrahydroprogesterone), is formulated with 15% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

10. The use of claim 1, wherein the allopregnanolone (3α,5α-tetrahydroprogesterone), is formulated with 30% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

11. A pharmaceutical dosage unit comprising complex of an allopregnanolone and a cyclodextrin.

12. The dosage unit of claim 11, wherein the allopregnanolone is selected from the group consisting of allopregnanolone and salts and enantomeric forms thereof.

13. The dosage unit of claim 11, wherein the cyclodextrin is selected from the group consisting of cyclic oligosaccharides containing or comprisingcomprising six (α-cyclodextrin), seven (β-cyclodextrin), eight (γ-cyclodextrin), or more α-(1,4)- linked glucose residues, and chemically modified cyclodextrins.

14. The dosage unit of claim 11, wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin; β-cyclodextrin; γ-cyclodextrin; methyl α-cyclodextrin; methyl β-cyclodextrin; methyl γ-cyclodextrin; ethyl β-cyclodextrin; butyl α-cyclodextrin; butyl β-cyclodextrin; butyl γ-cyclodextrin; pentyl γ-cyclodextrin; hydroxyethyl β-cyclodextrin; hydroxyethyl γ-cyclodextrin; 2-hydroxypropyl α-cyclodextrin; 2-hydroxypropyl β-cyclodextrin; 2-hydroxypropyl γ-cyclodextrin; 2-hydroxybutyl β-cyclodextrin; acetyl α-cyclodextrin; acetyl β-cyclodextrin; acetyl γ-cyclodextrin; propionyl β-cyclodextrin; butyryl β-cyclodextrin; succinyl α-cyclodextrin; succinyl β-cyclodextrin; succinyl γ-cyclodextrin; benzoyl β-cyclodextrin; palmityl β-cyclodextrin; toluenesulfonyl β-cyclodextrin; acetyl methyl β-cyclodextrin; acetyl butyl β-cyclodextrin; glucosyl α-cyclodextrin; glucosyl β-cyclodextrin; glucosyl γ-cyclodextrin; maltosyl α-cyclodextrin; maltosyl β-cyclodextrin; maltosyl γ-cyclodextrin; α-cyclodextrin carboxymethylether; β-cyclodextrin carboxymethylether; γ-cyclodextrin carboxymethylether; carboxymethylethyl β-cyclodextrin; phosphate ester α-cyclodextrin; phosphate ester β-cyclodextrin; phosphate ester γ-cyclodextrin; 3-trimethylammonium-2-hydroxypropyl β-cyclodextrin; sulfobutyl ether β-cyclodextrin; carboxymethyl α-cyclodextrin;

carboxymethyl β-cyclodextrin; carboxymethyl γ-cyclodextrin, alkyl cyclodextrins, hydroxy alkyl cyclodextrins, carboxy alkyl cyclodextrins and sulfoalkyl ether cyclodextrins, and combinations thereof.

15. The pharmaceutical dosage unit of claim 11 comprising a complex of 3α,5α-tetrahydroprogesterone with sulfobutylether-βcyclodextrin (SBEβCD).

16. The pharmaceutical dosage unit of claim 15 comprising 3α,5α-tetrahydroprogesterone formulated in sterile 0.9% sodium chloride containing or comprisingcomprising 6% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

17. The pharmaceutical dosage unit of claim 15 comprising 3α,5α-tetrahydroprogesterone formulated in sterile 0.9% sodium chloride comprising 15% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

18. The pharmaceutical dosage unit of claim 15 comprising 3α,5α-tetrahydroprogesterone formulated in sterile 0.9% sodium chloride comprising 30% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

19. Use of an effective amount of a dosage formulation of allopregnanolone in a cyclodextrin carrier in the manufacture of a medicament for treating a CNS disorder in a subject.

20. The use of claim 19, wherein the allopregnanolone is to be administered in a therapeutically effective two-level dosing regimen of allopregnanolone, including a first time period, wherein a first hourly dose of allopregnanolone is to be administered to the subject, followed by a second time period, wherein a lower hourly infusion dose of allopregnanolone is to be administered.

21. The use of claim 20, wherein the allopregnanolone is to be administered a loading dose administered over 1 hour followed by a maintenance infusion for the next 95 hours, and then tapered off by reducing the dose.

22. The use of claim 19, wherein the allopregnanolone is to be administered over a period of five days.

23. The use of claim 19, wherein the concentration of the allopregnanolone is between about 0.25 mg/mL and about 15 mg/mL.

24. The use of claim 19, wherein the concentration of the allopregnanolone is between about 1.5mg/mL.

25. The use of claim 19, wherein the dosage of allopregnanolone administered by infusion produces a steady-state serum allopregnanolone concentration between about 150 nM and 2500 nM.

26. The use of claim 19, wherein the allopregnanolone (3α,5α-tetrahydroprogesterone), is formulated with 6% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

27. The use of claim 19, wherein the allopregnanolone (3α,5α-tetrahydroprogesterone), is formulated with 15% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

28. The use of claim 19, wherein the allopregnanolone (3α,5α-tetrahydroprogesterone), is formulated with 30% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

29. The use of claim 19, wherein the CNS disorder is status epilepticus.

30. The use of claim 29, wherein the status epilepticus disorder is refractory status epilepticus.

26. The use of claim 19, wherein the status epilepticus disorder is non-convulsive status epilepticus.

27. The use of claim 19, wherein the CNS disorder is a traumatic brain injury.

28. The use of claim 19, wherein the CNS disorder is a seizure.

29. The use of claim 19, wherein the seizure is an acute repetitive seizure or a cluster seizure.

30. Use of an effective amount of a dosage formulation of allopregnanolone in the manufacture of a medicament for treating a CNS disorder in a subject, wherein the CNS disorder is a seizure or status epilepticus.

31. The use of claim 30, wherein the disorder is status epilepticus.

32. The use of claim 30, wherein the status epilepticus disorder is refractory status epilepticus.

33. The use of claim 30, wherein the status epilepticus disorder is non-convulsive status epilepticus.

34. The use of claim 30, wherein the allopregnanolone is to be administered in a therapeutically effective two-level dosing regimen of allopregnanolone, including a first time period, wherein a first hourly dose of allopregnanolone is to be administered to the subject, followed by a second time period, wherein a lower hourly infusion dose of allopregnanolone is to be administered.

35. The use of claim 34, wherein the allopregnanolone is to be administered a loading dose administered over 1 hour followed by a maintenance infusion for the next 95 hours, and then tapered off by reducing the dose.

36. The use of claim 30, wherein the allopregnanolone is to be administered over a period of five days.

37. The use of claim 30, wherein the concentration of the allopregnanolone is between about 0.25 mg/mL and about 15 mg/mL.

38. The use of claim 30, wherein the concentration of the allopregnanolone is between about 1.5mg/mL.

39. The use of claim 30, wherein the dosage of allopregnanolone administered by infusion produces a steady-state serum allopregnanolone concentration between about 150 nM and 2500 nM.

40. The use of claim 30, wherein the allopregnanolone (3α,5α-tetrahydroprogesterone), is formulated with 6% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

41. The use of claim 30, wherein the allopregnanolone (3α,5α-tetrahydroprogesterone), is formulated with 15% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).

42. The use of claim 30, wherein the allopregnanolone (3α,5α-tetrahydroprogesterone), is formulated with 30% pharmaceutical grade sulfobutylether-βcyclodextrin (SBEβCD).