CLAIMS

1. A method for treating tuberous sclerosis complex or tuberous sclerosis complex-related epilepsy comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutically acceptable pregnenolone neurosteroid or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the pregnenolone neurosteroid is ganaxolone.

3. The method of any one of the preceding claims, wherein the pregnenolone neurosteroid is administered three time per day.

4. The method of any one of claims 1-2, wherein the pregnenolone neurosteroid is administered twice per day.

5. The method of any one of the preceding claims, wherein the subject is administered from about 200 mg per day to about 1,800 mg per day of ganaxolone.

6. The method of any one of claims 1-4, wherein the subject is administered up to about 1,800 mg per day of ganaxolone.

7. The method of any preceding claim, wherein ganaxolone is administered about 1,500 mg per day of ganaxolone.

8. The method of any one of the preceding claims, wherein ganaxolone is administered in an amount of up to 63 mg/kg/day.

9. The method of any one of the preceding claims, wherein the pregnenolone neurosteroid is administered orally.

10. The method of any one of the preceding claims, wherein the pregnenolone neurosteroid is administered as an oral suspension.

11. The method of any one of the preceding claims, wherein the pregnenolone neurosteroid is administered as an oral capsule.

12. The method of any one of the preceding claims, wherein the tuberous sclerosis complex-related epilepsy is a infantile spasm.

13. The method of any one of the preceding claims, wherein the tuberous sclerosis complex-related epilepsy is a focal impaired awareness seizure.

14. The method of any one of the preceding claims, wherein the tuberous sclerosis complex-related epilepsy is a focal seizure.

15. The method of any one of the preceding claims, wherein the tuberous sclerosis complex-related epilepsy is a generalized seizure.

16. The method of any one of the preceding claims, wherein administering the pregnenolone neurosteroid reduces the frequency of seizure and/or severity of seizure in the subject relative to baseline.

17. The method of any one of the preceding claims, wherein administering the pregnenolone neurosteroid results in a reduction in seizure frequency of about 20% or greater relative to baseline seizure frequency.

18. The method of any one of the preceding claims, wherein administering the pregnenolone neurosteroid results in a reduction in seizure frequency of at least about 35% or greater relative to baseline seizure frequency.

19. The method of any one of the preceding claims, wherein the subject is monitored by electroencephalogram (EEG).

20. The method of any one of the preceding claims, wherein seizure activity in the subject is monitored by electroencephalogram (EEG).

21. The method of any one of the preceding claims, wherein ganaxolone is administered in amount sufficient to provide a ganaxolone plasma concentration in the subject of about 100 ng/mL for approximately 70% or more for a 24 hour-day .

22. The method of claim 21, wherein ganaxolone is administered three times a day.

23. The method of any one the preceding claims, further comprising:

measuring the level of an endogenous neurosteroid in the subject prior to administering the pregnanolone neurosteroid, wherein a subject having a low endogenous neurosteroid indicates that the subject will respond to the pregnanolone neurosteroid; and

administering a therapeutically effective amount of the pregnenolone neurosteroid to the subject having a low endogenous neurosteroid level.

24. The method of claim 23, wherein the endogenous neurosteroid is allopregnanolone-sulfate.

25. The method of any one of claims 23 or 24, wherein the low endogenous neurosteroid level is an amount of 2500 pg mL^{-1} or less.

26. The method of claim 25, wherein the pregnenolone neurosteroid is ganaxolone.

27. A method for treating tuberous sclerosis complex or tuberous sclerosis complex-related epilepsy comprising administering to a subject in need thereof ganaxolone in a therapeutically effective amount that produces a ganaxolone plasma concentration of at least about 100 ng/ml for at least about 70% or more for a period of a 24 hour-day.

28. The method of claim 27, wherein ganaxolone is administered three times per day.

29. The method of any one of claims 27 or 28, wherein ganaxolone is administered orally.

30. The method of any one of claims 27-29, wherein ganaxolone is administered as an oral suspension.

31. The method of any one of claims 27-29, wherein ganaxolone is administered as an oral capsule.

32. The method of any one of claims 27-31, wherein ganaxolone is administered in an amount of up to 63 mg/kg/day.

33. The method of any one of claims 27-32, wherein ganaxolone is administered in an amount of up to 1,800 mg per day.

34. The method of any one of claims 27-32, wherein ganaxolone is administered in an amount of up to 1,500 mg per day.

35. The method of any one of claims 27-34, wherein the tuberous sclerosis complex-related epilepsy is a infantile spasm, a focal impaired awareness seizure, a focal seizure, or a generalized seizure.

36. The method of any one of claims 27-35, wherein administering ganaxolone reduces the frequency of seizure and/or severity of seizure in the subject relative to baseline.

37. The method of any one of claims 27-35, wherein administering ganaxolone reduces major motor frequency in the subject relative to baseline.

38. The method of any one of claims 27-35, wherein administering ganaxolone results in a reduction in seizure frequency of about 20% or greater relative to baseline seizure frequency.

39. The method of any one of claims 27-35, wherein administering ganaxolone results in a reduction in seizure frequency of at least about 35% or greater relative to baseline seizure frequency.

40. The method of any one of claims 27-39, wherein the subject is monitored by electroencephalogram (EEG).

41. The method of any one of claims 27-39, wherein seizure activity in the subject is monitored by electroencephalogram (EEG).

42. A method of treating a subject having or suspected of having tuberous sclerosis-related epilepsy, comprising

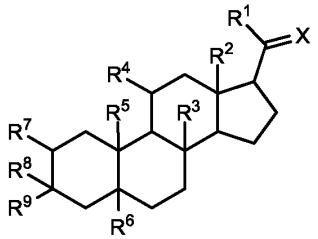
determining whether the subject has a low level of an endogenous neurosteroid; and

administering a therapeutically effective amount of a pharmaceutically acceptable pregnenolone neurosteroid or a pharmaceutically acceptable salt thereof to the subject if the subject has a low level of the endogenous neurosteroid.

43. The method of claim 42, wherein the endogenous neurosteroid is allopregnanolone-sulfate, and the pregnenolone neurosteroid is ganaxolone.

44. The method of any one of claims 42 or 43, wherein the endogenous neurosteroid is allopregnanolone-sulfate, and the low level of the endogenous stereoid is a level of 2500 pg mL^{-1} or less.

45. The method of any one of claims 42-44, wherein the pregnenolone neurosteroid is a compound of Formula IA:



Formula IA

or a pharmaceutically acceptable salt thereof, wherein:

X is O, S, or NR^{10};

R^1 is hydrogen, hydroxyl, $-CH_2A$, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, or optionally substituted arylalkyl;

A is hydroxyl, O, S, NR^{11}, optionally substituted nitrogen-containing five-membered heteroaryl, optionally substituted nitrogen-containing five-membered heteroaryl or optionally substituted nitrogen-containing bicyclic heteroaryl or bicyclic heterocyclyl,

R^4 is hydrogen, hydroxyl, oxo, optionally substituted alkyl, or optionally substituted heteroalkyl,

R^2, R^3, R^5, R^6, and R^7 are each independently absent, hydrogen, hydroxyl, halogen, optionally substituted a C_1-C_6 alkyl, optionally substituted a C_1-C_6alkoxyl (e.g., methoxyl) or optionally substituted heteroalkyl;

R^8 and R^9 are each independently selected from a group consisting of hydrogen, a C_1-C_6 alkyl (e.g., methyl), a halogenated C_1-C_6 alkyl (e.g., trifluoromethyl) or C_1-C_6alkoxyl (e.g., methoxyl), or R^8 and R^9 form an oxo group;

R^{10} is hydrogen, hydroxyl, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, or optionally substituted arylalkyl where each alkyl is a C_1-C_{10}alkyl, C_3-C_6cycloalkyl, (C_3-C_6cycloalkyl)C_1-C_4alkyl, and optionally contains a single bond replaced by a double or triple bond;

each heteroalkyl group is an alkyl group in which one or more methyl group is replaced by an independently chosen -O-, -S-, -N(R^{10})-, -S(=O)- or -S(=O)$_2$-, where R^{10} is hydrogen, alkyl, or alkyl in which one or more methylene group is replaced by -O-, -S-, -NH, or -N-alkyl;

R^{11} is -H_2 or –HR^{12};

R^{12} is C_1-C_6 alkyl or C_1-C_6 alkoxy.

46. The method of claim 45, wherein the pregnenolone neurosteroid is selected from the group consisting of allopregnanolone, pregnenolone, 5-alphaDHP (5-alphadihydroprogesterone), pregnanolone, dehydroepiandrosterone (DHEA), ganaxolone, 3α-Hydroxy-3β-methyl-21-(4-cyano-1*H*-pyrazol-1'-yl)-19-nor-5β-pregnan-20-one, pharmaceutically acceptable salts of any of the foregoing, and combinations of any of the foregoing.

47. The method of any one of claims 42-46, wherein the pregnenolone neurosteroid is administered orally.

48. The method of any one of claims 42-47, wherein the subject is administered up to about 63 mg/kg/day of ganaxolone.

49. The method of claim 48, wherein the subject is administered up to about 33 mg/kg/day of ganaxolone.

50. The method of any one of claims 42-47, wherein the subject is administered up to about 1,800 mg per day of ganaxolone.

51. The method of any one of claims 42-47, wherein the subject is administered up to about 1,500 mg per day of ganaxolone.

52. The method of claim 42-51, wherein the tuberous sclerosis complex-related epilepsy is selected from the group consisting of a focal motor seizure, a focal seizure, and a generalized seizure.

53. The method of any one of claims 42-52, wherein administering ganaxolone reduces the frequency of seizure and/or severity of seizure in the subject relative to baseline.

54. The method of any one of claims 42-53, wherein administering ganaxolone reduces major motor frequency in the subject relative to baseline.

55. The method of any one of claims 42-53, wherein administering ganaxolone results in a reduction in seizure frequency of about 20% or greater relative to baseline seizure frequency.

56. The method of any one of claims 42-53, wherein administering ganaxolone results in a reduction in seizure frequency of at least about 35% or greater relative to baseline seizure frequency.

57. The method of any one of claims 42-56, wherein the subject is monitored by electroencephalogram (EEG).

58. The method of any one of claims 42-56, wherein seizure activity in the subject is monitored by electroencephalogram (EEG).

59. The method of claim 42, wherein the endogenous neurosteroid is allopregnanolone, and a low level of allopregnanolone is a 200 pg mL^{-1} or less.

60. The method of claim 42, wherein the endogenous neurosteroid comprises allopregnanolone, allopregnanolone-sulfate, pregnenolone, pregnenolone-sulfate, and mixtures thereof.