compliance and, thus, benefit patients with diseases or conditions involving T-type calcium channels, including, for example, essential tremor.

SUMMARY

[00010] Described herein are methods of preventing and/or treating a disease or condition relating to aberrant function or activity of T-type calcium channels, such as psychiatric disorders (e.g., mood disorder (e.g., major depressive disorder)), pain, tremor (e.g., essential tremor), seizures (e.g., absence seizures), epilepsy, or an epilepsy syndrome (e.g., juvenile myoclonic epilepsy). Also disclosed herein are methods for modulating the function of a T-type calcium channel and methods of administering a titrated dosage of a T-type calcium channel antagonist, such as the compound of formula (I) or a pharmaceutically acceptable salt thereof.

[0010a] In one aspect, the present disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or condition relating to aberrant function or activity of a T-type calcium channel in a subject in need thereof, wherein the use comprises: (a) a first dose of the compound of formula (I) or a pharmaceutically acceptable salt thereof is to be administered to the subject for a first period of time, wherein following administration of the first dose of the compound for the first period of time, the subject has a maximum plasma drug concentration (C_{max}) ranging from 30 ng/mL to 130 ng/mL and/or an area under the plasma concentration-time curve from time of administration to 24 hours after administration (AUC_{24}) ranging from 490 ng*h/mL to 2030 ng*h/mL; (b) the amount of the compound in the first dose is increased and one or more increased doses of the compound is to be administered to the subject to arrive at a maximum titrated dose; and (c) the maximum titrated dose of the compound is to be administered to the subject to maintain in the subject a C_{max} ranging from 280 ng/mL to 470 ng/mL and/or an AUC_{24} ranging from 3480 ng*h/mL to 5800 ng*h/mL. In yet another aspect, the present disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or condition relating to aberrant function or activity of a T-type calcium channel in a subject in need thereof, wherein the use comprises: (a) a first dose of the compound of formula (I) or a pharmaceutically acceptable salt thereof is to be administered to the subject for a first period of time in an amount ranging from 5 mg to 40 mg per day; (b) the amount of the compound in the first dose is increased and one or more increased doses of the compound is to be administered to the subject to arrive at a maximum titrated dose; and (c) the maximum titrated dose of the compound is to be administered to the subject in an amount ranging from 20 mg to 120 mg per day.

[00011] In one ~~aspect~~example, the methods of treating a disease or condition relating to aberrant function or activity of a T-type calcium channel in a subject in need thereof comprise (a) administering a first dose of a compound of formula (I) or a pharmaceutically acceptable salt thereof to the subject for a first period of time, wherein following administration of the first dose of the compound for the first period of time the subject has a maximum plasma drug concentration (C_{max}) ranging from about 30 ng/mL to about 130 ng/mL and/or an area under the plasma concentration-time curve from time of administration to 24 hours after administration (AUC_{24}) ranging from about 490 ng*h/mL to about 2030 ng*h/mL; (b) increasing the amount of the compound in the first dose and administering one or more increased doses of the compound to the subject to arrive at a maximum titrated dose; and (c) administering the maximum titrated dose of the compound to the subject to maintain in the subject a C_{max} ranging from about 280 ng/mL to about 470 ng/mL and/or an AUC_{24} ranging from about 3480 ng*h/mL to about 5800 ng*h/mL. Typically, each dose is administered once daily; however, the frequency of administration may be altered as long as the desired C_{max} and/or AUC_{24} values are achieved, as discussed in other sections of this application.

[00012] In certain ~~aspect~~examples, step (b) comprises increasing the first dose to a second dose and administering the second dose of the compound to the subject for a second period of time, wherein following administration of the second dose of the compound for the second period of time, the subject has a C_{max} ranging from about 80 ng/mL to about 300 ng/mL and/or an AUC_{24} ranging from about 1220 ng*h/mL to about 4070 ng*h/mL. In certain ~~aspect~~examples, step (b) comprises increasing the first dose to a second dose and administering the second dose of the compound to the subject for a second period of time, wherein following administration of the second dose of the compound for the second period of time, the subject has a C_{max} ranging from about 80 ng/mL to about 220 ng/mL and/or an AUC_{24} ranging from about 1220 ng*h/mL to about 3330

ng*h/mL; and increasing the second dose to a third dose and administering the third dose of the compound to the subject for a third period of time, wherein following administration of the third dose of the compound for the third period of time, the subject has a C_{max} ranging from about 180 ng/mL to about 380 ng/mL and/or an AUC_{24} ranging from about 2440 ng*h/mL to about 4700 ng*h/mL.

[00013] In various other ~~aspect~~examples disclosed herein, step (b) comprises: (i) increasing the first dose to a second dose and administering the second dose of the compound to the subject for a second period of time, wherein following administration of the second dose of the compound for the second period of time, the subject has a C_{max} ranging from about 80 ng/mL to about 130 ng/mL and/or an AUC_{24} ranging from about 1220 ng*h/mL to about 2030 ng*h/mL; (ii) increasing the second dose to a third dose and administering the third dose of the compound to the subject for a third period of time, wherein following administration of the third dose of the compound for the third period of time, the subject has a C_{max} ranging from about 130 ng/mL to about 220 ng/mL and/or an AUC_{24} ranging from about 2000 ng*h/mL to about 3330 ng*h/mL; (iii) increasing the third dose to a fourth dose and administering the fourth dose of the compound to the subject for a fourth period of time, wherein following administration of the fourth dose of the compound for the fourth period of time, the subject has a C_{max} ranging from about 180 ng/mL to about 300 ng/mL and/or an AUC_{24} ranging from about 2440 ng*h/mL to about 4070 ng*h/mL; and (iv) increasing the fourth dose to a fifth dose and administering the fifth dose of the compound to the subject for a fifth period of time, wherein following administration of the fifth dose of the compound for the fifth period of time, the subject has a C_{max} ranging from about 230 ng/mL to about 380 ng/mL and/or an AUC_{24} ranging from about 2820 ng*h/mL to about 4700 ng*h/mL.

[00014] Further disclosed herein are methods of treating a disease or condition relating to aberrant function or activity of a T-type calcium channel in a subject in need thereof, the method comprising (a) administrating a first dose of a compound of formula (I) or a pharmaceutically acceptable salt thereof to the subject for a first period of time in an amount ranging from about 5 mg to about 40 mg per day; (b) increasing the amount of the compound in the first dose and administering one or more increased doses of the compound to the subject to arrive at a maximum titrated dose; and (c) administrating the maximum titrated dose of the compound to the subject in an amount ranging from about 20 mg to about 120 mg per day.

[00015] In certain ~~aspect~~examples disclosed herein, step (b) comprises increasing the first dose to a second dose and administering the second dose of the compound to the subject for a second period of time in an amount ranging from about 40 mg per day to about 80 mg per day, and in

various other ~~aspect~~examples, step (b) comprises increasing the first dose to a second dose and administering the second dose of the compound to the subject for a second period of time in an amount ranging from about 40 mg per day to about 60 mg per day; and increasing the second dose to a third dose and administering the third dose of the compound to the subject for a third period of time in an amount ranging from about 80 mg per day to about 100 mg per day.

[00016] In one ~~aspect~~example of all methods, each of the first period, second period, and third period ranges from about 3 to about 9 days, such as about 3 to about 7 days, and in one ~~aspect~~example, each of the first period, second period, and third period is 3 days. In a further ~~aspect~~example disclosed herein, each of the first period and second period is 3 days and the third period is 7 days.

[00017] In one ~~aspect~~example of the disclosure, in the first period, the compound is administered in an amount ranging from about 20 mg to about 40 mg per day, such as about 20 mg per day or about 40 mg per day. In certain ~~embodiment~~examples, in the second period, the compound is administered in an amount ranging from about 40 mg to about 80 mg per day, such as about 40 mg per day, about 60 mg per day, or about 80 mg per day. In further ~~embodiment~~examples, in the third period, the compound is administered in an amount ranging from about 60 mg to about 120 mg per day, such as about 60 mg per day, about 80 mg per day, about 100 mg per day, or about 120 mg per day. In certain ~~embodiment~~examples, a second dose is increased no more than 40 mg per day relative to the first dose and/or a third dose is increased no more than 40 mg per day relative to the second dose.

[00018] In certain ~~aspect~~examples, the methods disclosed herein further comprise increasing the third dose to a fourth dose and administering the fourth dose of the compound to the subject for a fourth period of time in an amount of about 120 mg per day. In certain ~~aspect~~examples, the methods comprise increasing a first dose of about 20 mg per day administered for a first time period of about 3 days to a second dose and administering the second dose of the compound to the subject for a second period of time in an amount of about 40 mg per day.

[00019] In certain ~~aspect~~examples, in the methods disclosed herein wherein the second period is 3 days and the compound is administered in an amount of about 40 mg per day, the methods further comprise in step (b) increasing the second dose to a third dose and administering the third dose of the compound to the subject for a third period of time in an amount of about 60 mg per day; increasing the third dose to a fourth dose and administering the fourth dose of the compound to the subject for a fourth period of time in an amount of about 80 mg per day; and increasing the fourth dose to a fifth dose and administering the fifth dose of the compound to the subject for a fifth period of time in an amount of about 100 mg per day, wherein the maximum titrated dose of the compound is about 120 mg per day.

[00020] In certain ~~aspect~~examples of the methods disclosed herein, the first period is 3 days and the compound is administered in an amount of about 20 mg per day, and the second period is about 3 days and the compound is administered in an amount of about 40 mg per day. In certain ~~embodiment~~examples, the third period is 3 days and the compound is administered in an amount of about 80 mg per day, and the method further comprises administering to the subject for a fourth period about 120 mg of the compound per day.

[00021] In certain ~~aspect~~examples of the methods disclosed herein, the first period is 3 days and the compound is administered in an amount of about 20 mg per day, the second period is 3 days and the compound is administered in an amount of about 40 mg per day, the third period is 7 days and the compound is administered in an amount of about 60 mg per day, and the method further comprises (d) administering to the subject for a fourth period ranging from about 3 to about 9 days about 80 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof per day, (e) administering to the subject for a fifth period ranging from about 3 to about 9 days about 100 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof per day; and (f) administering to the subject for a sixth period about 120 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof per day.

[00022] In various ~~aspect~~examples of the disclosure, the pharmaceutically acceptable salt is a hydrochloride salt of formula (II). In certain ~~aspect~~examples, the subject is a human aged 18 to 55 years old, and in certain ~~aspect~~examples the subject is a human aged 55 to 75 years.

[00023] In certain ~~aspect~~examples, the disease or condition relating to aberrant function or activity of T-type calcium channels is a psychiatric disorder, pain, tremor, seizures, epilepsy, or epilepsy syndrome. In certain ~~aspect~~examples, the disorder is tremor, such as essential tremor. In certain ~~embodiment~~examples, the compound of formula (I) or a pharmaceutically acceptable salt thereof is in a modified release dosage formulation comprising at least one modified release polymer, such as a modified release polymer chosen from hydroxypropyl methylcellulose, ethylcellulose, and polyacrylate polymers. In certain ~~aspect~~examples of all ~~embodiment~~examples disclosed herein, the pharmaceutically acceptable salt of formula (II) is crystalline Form C, and in certain ~~aspect~~examples, the pharmaceutically acceptable salt of formula (II) is crystalline Form B.

[00024] In certain ~~aspect~~examples of the methods disclosed herein, the method results in an EEG sigma frequency band reduction during non-rapid eye movement (NREM) sleep and/or an EEG gamma frequency band reduction during the awake state in an eyes open (EO) condition or an eyes closed (EC) condition in the subject. In certain ~~embodiment~~examples, a ratio of the NREM sigma frequency band after administration of a dosage to a NREM sigma frequency band baseline ranges from about 0.4 to about 0.7, such as a ratio of from about 0.5 to about 0.6. In certain

~~embodiment~~examples, the methods disclosed herein result in a NREM sigma frequency reduction in the subject when the subject is administered a dosage of the compound of formula (I) or a pharmaceutically acceptable salt thereof resulting in a C_{max} of about 5 ng/mL to about 470 ng/mL, such as a C_{max} of about 180 to about 300 ng/mL. In certain ~~embodiment~~examples, the methods disclosed herein result in a NREM sigma frequency reduction in the subject when the subject is administered a dosage of the compound of formula (I) or a pharmaceutically acceptable salt thereof resulting in a C_{ave} during the EEG recording of about 10 ng/mL to about 200 ng/mL, such as a C_{ave} of about 12 to about 150 ng/mL. In certain ~~embodiment~~examples, the methods disclosed herein result in an EO or EC gamma frequency band reduction in the subject when the subject is administered a dosage of the compound of formula (I) or a pharmaceutically acceptable salt thereof resulting in a C_{max} of the compound of about 30 ng/mL to about 470 ng/mL, such as a C_{max} of about 280 to about 470 ng/mL. In certain ~~embodiment~~examples, the methods disclosed herein result in an EO or EC gamma frequency band reduction in the subject when the subject is administered a dosage of the compound of formula (I) or a pharmaceutically acceptable salt thereof resulting in a plasma concentration of about 75 ng/ml to about 310 ng/mL, such as a plasma concentration of about 90 to about 190 ng/mL.

[00025] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing Brief Description of the Figures, Detailed Description, Examples, and Claims.

BRIEF DESCRIPTION OF THE FIGURES

[00026] FIG. 1 is a X-ray Powder Diffraction (XRPD) pattern of Form C of the compound of formula (II).

[00027] FIG. 2 is a differential scanning calorimetry (DSC) thermogram of Form C of the compound of formula (II).

[00028] FIG. 3 is a thermogravimetric analysis (TGA) thermogram of Form C of the compound of formula (II).

[00029] FIG. 4 are hot stage microscopy (HSM) photomicrographs of Form C of the compound of formula (II).

[00030] FIG. 5 is a graph showing mean concentration-time profiles of the compound of formula (II) after single 20 mg oral doses of the modified-release tablets (formulation 1, formulation 2, and formulation 3) and immediate-release (IR) capsule of the compound of formula (II).

CLAIMS

1. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for ~~A method of~~ treating a disease or condition relating to aberrant function or activity of a T-type calcium channel in a subject in need thereof, wherein the ~~method~~ use comprises~~ing~~:

(a) ~~administering~~ a first dose of ~~a~~ the compound of formula (I) or a pharmaceutically acceptable salt thereof is to be administered to the subject for a first period of time, wherein following administration of the first dose of the compound for the first period of time, the subject has a maximum plasma drug concentration (C_{max}) ranging from ~~about~~ 30 ng/mL to ~~about~~ 130 ng/mL and/or an area under the plasma concentration-time curve from time of administration to 24 hours after administration (AUC_{24}) ranging from ~~about~~ 490 ng*h/mL to ~~about~~ 2030 ng*h/mL;

(b) ~~increasing~~ the amount of the compound in the first dose is increased and ~~administering~~ one or more increased doses of the compound is to be administered to the subject to arrive at a maximum titrated dose; and

(c) ~~administering~~ the maximum titrated dose of the compound is to be administered to the subject to maintain in the subject a C_{max} ranging from ~~about~~ 280 ng/mL to ~~about~~ 470 ng/mL and/or an AUC_{24} ranging from ~~about~~ 3480 ng*h/mL to ~~about~~ 5800 ng*h/mL.

2. The ~~method~~ use of claim 1, wherein the first period of time ranges from ~~about~~ 3 to ~~about~~ 9 days.

3. The ~~method~~ use of claim 1 or 2, wherein step (b) comprises that:

(i) ~~increasing~~ the first dose is increased to a second dose and ~~administering~~ the second dose of the compound is to be administered to the subject for a second period of time, wherein following administration of the second dose of the compound for the second period of time, the subject has a C_{max} ranging from ~~about~~ 80 ng/mL to ~~about~~ 300 ng/mL and/or an AUC_{24} ranging from ~~about~~ 1220 ng*h/mL to ~~about~~ 4070 ng*h/mL

(ii) the first dose is increased to a second dose and the second dose of the compound is to be administered to the subject for a second period of time, wherein following administration of the second dose of the compound for the second period of time, the subject has a C_{max} ranging from 80 ng/mL to 220 ng/mL and/or an AUC_{24} ranging from 1220 ng*h/mL to 3330 ng*h/mL; and

the second dose is increased to a third dose and the third dose of the compound is to be administered to the subject for a third period of time, wherein following administration of the

third dose of the compound for the third period of time, the subject has a C_{max} ranging from 180 ng/mL to 380 ng/mL and/or an AUC_{24} ranging from 2440 ng*h/mL to 4700 ng*h/mL; or

(iii) the first dose is increased to a second dose and the second dose of the compound is to be administered to the subject for a second period of time, wherein following administration of the second dose of the compound for the second period of time, the subject has a C_{max} ranging from 80 ng/mL to less than 130 ng/mL and/or an AUC_{24} ranging from 1220 ng*h/mL to less than 2030 ng*h/mL;

the second dose is increased to a third dose and the third dose of the compound is to be administered to the subject for a third period of time, wherein following administration of the third dose of the compound for the third period of time, the subject has a C_{max} ranging from 130 ng/mL to less than 220 ng/mL and/or an AUC_{24} ranging from 2000 ng*h/mL to less than 3330 ng*h/mL;

the third dose is increased to a fourth dose and the fourth dose of the compound is to be administered to the subject for a fourth period of time, wherein following administration of the fourth dose of the compound for the fourth period of time, the subject has a C_{max} ranging from 180 ng/mL to less than 300 ng/mL and/or an AUC_{24} ranging from 2440 ng*h/mL to less than 4070 ng*h/mL; and

the fourth dose is increased to a fifth dose and the fifth dose of the compound is to be administered to the subject for a fifth period of time, wherein following administration of the fifth dose of the compound for the fifth period of time, the subject has a C_{max} ranging from 230 ng/mL to less than 380 ng/mL and/or an AUC_{24} ranging from 2820 ng*h/mL to less than 4700 ng*h/mL.

~~4. The method of claim 1 or 2, wherein step (b) comprises:~~

~~increasing the first dose to a second dose and administering the second dose of the compound to the subject for a second period of time, wherein following administration of the second dose of the compound for the second period of time, the subject has a C_{max} ranging from about 80 ng/mL to about 220 ng/mL and/or an AUC_{24} ranging from about 1220 ng*h/mL to about 3330 ng*h/mL; and~~

~~increasing the second dose to a third dose and administering the third dose of the compound to the subject for a third period of time, wherein following administration of the third dose of the compound for the third period of time, the subject has a C_{max} ranging from about 180 ng/mL to about 380 ng/mL and/or an AUC_{24} ranging from about 2440 ng*h/mL to about 4700 ng*h/mL.~~

~~5~~4. The ~~method~~ use of any one of claims 1-~~4~~3, wherein the second dose is increased no more than 40 mg relative to the first dose and wherein the third dose is increased no more than 40 mg relative to the second dose.

~~6~~5. The ~~method~~ use of claim 3 or~~,~~ 4, ~~or 5~~ wherein in (i) or (ii) the second period of time and the third period of time range from 3 to 9 days; or
wherein in (iii), the first period of time, the second period of time, the third period of time, the fourth period of time, and the fifth period of time range from 3 to 9 days.

~~7. The method of claim 1, wherein step (b) comprises:~~

~~increasing the first dose to a second dose and administering the second dose of the compound to the subject for a second period of time, wherein following administration of the second dose of the compound for the second period of time, the subject has a C_{max} ranging from about 80 ng/mL to less than 130 ng/mL and/or an AUC_{24} ranging from about 1220 ng*h/mL to less than 2030 ng*h/mL;~~

~~increasing the second dose to a third dose and administering the third dose of the compound to the subject for a third period of time, wherein following administration of the third dose of the compound for the third period of time, the subject has a C_{max} ranging from 130 ng/mL to less than 220 ng/mL and/or an AUC_{24} ranging from 2000 ng*h/mL to less than 3330 ng*h/mL;~~

~~increasing the third dose to a fourth dose and administering the fourth dose of the compound to the subject for a fourth period of time, wherein following administration of the fourth dose of the compound for the fourth period of time, the subject has a C_{max} ranging from 180 ng/mL to less than 300 ng/mL and/or an AUC_{24} ranging from 2440 ng*h/mL to less than 4070 ng*h/mL; and~~

~~increasing the fourth dose to a fifth dose and administering the fifth dose of the compound to the subject for a fifth period of time, wherein following administration of the fifth dose of the compound for the fifth period of time, the subject has a C_{max} ranging from 230 ng/mL to less than 380 ng/mL and/or an AUC_{24} ranging from 2820 ng*h/mL to less than 4700 ng*h/mL.~~

~~8. The method of claim 7, wherein the first period of time, the second period of time, the third period of time, the fourth period of time, and the fifth period of time range from 3 to 9 days.~~

~~9~~6. The ~~method~~ use of any one of claims 1-~~8~~5, wherein the first dose is 20 mg per day; or the maximum titrated dose is 120 mg per day; or each dose of a compound of formula (I) or a pharmaceutically acceptable salt thereof is to be administered to the subject daily.

~~10. The method of any one of claims 1-9, wherein the maximum titrated dose is 120 mg per day.~~

~~11. The method of any one of claims 1-9, wherein each dose of a compound of formula (I) or a pharmaceutically acceptable salt thereof is administered to the subject daily.~~

~~12~~7. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for ~~A method of~~ treating a disease or condition relating to aberrant function or activity of a T-type calcium channel in a subject in need thereof, wherein the ~~method~~ use comprises~~ing~~:

(a) ~~administering~~ a first dose of ~~a~~ the compound of formula (I) or a pharmaceutically acceptable salt thereof is to be administered to the subject for a first period of time in an amount ranging from ~~about~~ 5 mg to ~~about~~ 40 mg per day;

(b) ~~increasing~~ the amount of the compound in the first dose is increased and ~~administering~~ one or more increased doses of the compound is to be administered to the subject to arrive at a maximum titrated dose; and

(c) ~~administering~~ the maximum titrated dose of the compound is to be administered to the subject in an amount ranging from ~~about~~ 20 mg to ~~about~~ 120 mg per day.

~~13~~8. The ~~method~~ use of claim ~~12~~7, wherein the first period of time is 3 days.

~~14~~9. The ~~method~~ use of claim ~~12~~ 7 or ~~13~~8, wherein in step (b), the one or more increased doses of the compound are to be administered for a period of time ranging from 3 days to 7 days.

~~15~~10. The ~~method~~ use of any one of claims ~~12~~7-~~14~~9, wherein in the first period of time, the compound is to be administered in an amount ranging from ~~about~~ 20 mg to ~~about~~ 40 mg per day.

~~16~~11. The ~~method~~ use of any one of claims ~~12~~7-~~15~~10, wherein step (b) comprises that:

(i) ~~increasing~~ the first dose is increased to a second dose and ~~administering~~ the second dose of the compound is to be administered to the subject for a second period of time in an amount ranging from ~~about~~ 40 mg to ~~about~~ 80 mg per day; or

(ii) the first dose is increased to a second dose and the second dose of the compound is to be administered to the subject for a second period of time in an amount ranging from 40 mg to 60 mg per day; and

the second dose is increased to a third dose and the third dose of the compound is to be administered to the subject for a third period of time in an amount ranging from 80 to 100 mg per day.

~~17. The method of any one of claims 12-15, wherein step (b) comprising increasing the first dose to a second dose and administering the second dose of the compound to the subject for a second period of time in an amount ranging from about 40 mg to about 60 mg per day; and~~

~~increasing the second dose to a third dose and administering the third dose of the compound to the subject for a third period of time in an amount ranging from about 80 to about 100 mg per day.~~

~~18~~12. The ~~method~~ use of any one of claim ~~17~~11, wherein (ii) further ~~comprising~~ comprises that ~~increasing~~ the third dose is increased to a fourth dose and ~~administering~~ the fourth dose of the compound is to be administered to the subject for a fourth period of time in an amount of about 120 mg per day; or wherein in (ii) the third period is 3 days and the compound is to be administered in an amount of about 80 mg per day.

~~19~~13. The ~~method~~ use of claim ~~12~~7, wherein the first period is 3 days and the compound is to be administered in an amount of about 20 mg per day, and wherein step (b) comprises that ~~increasing~~ the first dose is increased to a second dose and ~~administering~~ the second dose of the compound is to be administered to the subject for a second period of time in an amount of about 40 mg per day.

~~20. The method of claim 17 or 18, wherein the third period is 3 days and the compound is administered in an amount of about 80 mg per day.~~

~~21~~14. The ~~method~~ use of claim ~~16~~11, wherein the second period is 3 days and the compound is to be administered in an amount of about 40 mg per day, and further ~~comprising~~ comprises that in step (b):

~~increasing~~ the second dose is increased to a third dose and ~~administering~~ the third dose of the compound is to be administered to the subject for a third period of time in an amount of about 60 mg per day;

i~~ncreasing~~ the third dose is increased to a fourth dose and ~~administering~~ the fourth dose of the compound is to be administered to the subject for a fourth period of time in an amount of about 80 mg per day; and

~~increasing~~ the fourth dose is increased to a fifth dose and ~~administering~~ the fifth dose of the compound is to be administered to the subject for a fifth period of time in an amount of about 100 mg per day,

wherein the maximum titrated dose of the compound is about 120 mg per day.

~~22~~15. The ~~method~~ use of any one of claims 1-~~21~~14, wherein the pharmaceutically acceptable salt is a hydrochloride salt of formula (II).

~~23~~16. The ~~method~~ use of any one of claims 1-~~22~~15, wherein the ~~the~~ disease or condition relating to aberrant function or activity of a T-type calcium channel is a psychiatric disorder, pain, tremor, seizures, epilepsy, or an epilepsy syndrome.

~~24~~17. The ~~method~~ use of claim ~~23~~16, wherein the disease or condition relating to aberrant function or activity of a T-type calcium channel is tremor.

~~25~~18. The ~~method~~ use of claim ~~24~~17, wherein the disease or condition relating to aberrant function or activity of a T-type calcium channel is essential tremor.

~~26~~19. The ~~method~~ use of any one of claims 1-~~25~~18, wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof is in a modified release dosage formulation comprising at least one modified release polymer.

~~27~~20. The ~~method~~ use of claim ~~26~~19, wherein about 80% of the compound of formula (I) or a pharmaceutically acceptable salt thereof is released within 7 hours upon administration to the subject.

~~28~~21. The ~~method~~ use of claim ~~26~~ 19 or ~~27~~20, wherein the modified release polymer is hydroxypropyl methylcellulose, ethylcellulose, or a polyacrylate polymer.

~~29~~22. The ~~method~~ use of any one of claims ~~26~~19-~~28~~21, wherein the modified release polymer is hydroxypropyl methylcellulose.

~~30~~23. The ~~method~~ use of any one of claims 1-22~~29~~, wherein the ~~method~~ use results in an EEG sigma frequency band reduction during NREM sleep in the subject.

~~31~~24. The ~~method~~ use of claim ~~30~~23, wherein a ratio of the EEG sigma frequency band reduction to an EEG sigma frequency band baseline during NREM sleep in the subject ranges from ~~about~~ 0.4 to ~~about~~ 0.7.