SUMMARY

[0006] Provided is a method of administering a vesicular monoamine transporter 2 (VMAT2) inhibitor to a subject in need thereof, wherein the subject has severe renal impairment, comprising: administering the VMAT2 inhibitor to the subject in need thereof.

[0007] Also provided is a method of administering a vesicular monoamine transporter 2 (VMAT2) inhibitor to a subject in need thereof, comprising: administering the VMAT2 inhibitor to the subject in need thereof, subsequently determining that the subject has severe renal impairment, and continuing administration of the VMAT2 inhibitor.

[0008] Also provided is a method of administering a vesicular monoamine transporter 2 (VMAT2) inhibitor to a subject in need thereof, wherein the subject has mild or moderate renal impairment, comprising: administering the VMAT2 inhibitor to the subject in need thereof, subsequently determining that the subject has severe renal impairment, and continuing administration of the VMAT2 inhibitor.

[0009] Also provided is a method of treating a disease or disorder requiring a vesicular monoamine transporter 2 (VMAT2) inhibitor in a subject in need thereof, wherein the subject has severe renal impairment, comprising: administering the VMAT2 inhibitor to the subject in need thereof.

[0010] Also provided is a method of treating a neurological or psychiatric disease or disorder in a subject in need thereof, comprising: administering a vesicular monoamine transporter 2 (VMAT2) inhibitor to the subject in need thereof, wherein the subject has severe renal impairment.

[0010a] In one aspect, the present disclosure provides use of a therapeutically effective amount of vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating a patient with a neurological or psychiatric disease or disorder, wherein the patient has severe renal impairment, and wherein the therapeutically effective amount is the same amount that would be administered to a patient with normal renal function.

[0010b] In another aspect, the present disclosure provides use of a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating a patient with a neurological or psychiatric disease or disorder, wherein:

(a) a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof is to be orally administered to the patient;

(b) the patient is subsequently determined to have severe renal impairment; and

(c) administration of the same therapeutically effective amount of the VMAT2 inhibitor is to be continued.

[0011] In some ~~embodiment~~examples, the VMAT2 inhibitor is chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts and/or isotopic variants thereof. In some ~~embodiment~~examples, the VMAT2 inhibitor is chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof. In some ~~embodiment~~examples, the VMAT2 inhibitor is a tosylate salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester. In some ~~embodiment~~examples, the VMAT2 inhibitor is a ditosylate salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-

2-yl ester. In some ~~embodiment~~examples, the ditosylate salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester is in crystalline Form I.

[0012] In some ~~embodiment~~examples, the VMAT2 inhibitor is an isotopic variant that is L-Valine, (2R,3R,11bR)-1,3,4,6,7,11b-hexahydro-9,10-di(methoxy-d3)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-yl ester or a pharmaceutically acceptable salt thereof.

[0013] In some ~~embodiment~~examples, the VMAT2 inhibitor is tetrabenazine (9,10-dimethoxy-3-isobutyl-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one), or a pharmaceutically acceptable salt and/or isotopic variant thereof. In some ~~embodiment~~examples, tetrabenazine is chosen from the RR, SS, RS, and SR isomers of tetrabenazine, and mixtures thereof. In some ~~embodiment~~examples, tetrabenazine is a mixture of the RR and SS isomers.

[0014] In some ~~embodiment~~examples, the VMAT2 inhibitor is deutetrabenazine.

[0015] In some ~~embodiment~~examples, the VMAT2 inhibitor is chosen from dihydrotetrabenazine (2-hydroxy-3-(2-methylpropyl)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-benzo(a)quinolizine), or a pharmaceutically acceptable salt and/or isotopic variant thereof. In some ~~embodiment~~examples, dihydrotetrabenazine is chosen from the RRR, SSS, SSRR, RSS, SSR, RRS, RSR, and SRS isomers of dihydrotetrabenazine, and mixtures thereof. In some ~~embodiment~~examples, the VMAT2 inhibitor is the RRR isomer ((+)-α-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol), or a pharmaceutically acceptable salt and/or isotopic variant thereof.

[0016] These and other aspects of the ~~invention~~disclosure will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information, procedures, compounds, and/or compositions, and are each hereby incorporated by reference in their entirety.

BRIEF DISCRIPTION OF THE FIGURE

[0017] FIG. 1 depicts the effects of hepatic impairment and severe renal impairment on valbenazine pharmacokinetics.

DETAILED DESCRIPTION

[0018] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known

What is claimed is:

CLAIMS:

~~1. A method of administering a vesicular monoamine transporter 2 (VMAT2) inhibitor to a subject in need thereof, wherein the subject has severe renal impairment, comprising:~~

~~administering the VMAT2 inhibitor to the subject in need thereof.~~

~~2. A method of administering a vesicular monoamine transporter 2 (VMAT2) inhibitor to a subject in need thereof, comprising:~~

~~administering the VMAT2 inhibitor to the subject in need thereof,~~

~~subsequently determining that the subject has severe renal impairment, and~~

~~continuing administration of the VMAT2 inhibitor.~~

~~3. A method of administering a vesicular monoamine transporter 2 (VMAT2) inhibitor to a subject in need thereof, wherein the subject has mild or moderate renal impairment, comprising:~~

~~administering the VMAT2 inhibitor to the subject in need thereof,~~

~~subsequently determining that the subject has severe renal impairment, and~~

~~continuing administration of the VMAT2 inhibitor.~~

~~4. A method of treating a disease or disorder requiring a vesicular monoamine transporter 2 (VMAT2) inhibitor in a subject in need thereof, wherein the subject has severe renal impairment, comprising:~~

~~administering theVMAT2 inhibitor to the subject in need thereof.~~

~~5.~~1. ~~A method of~~ Use of a therapeutically effective amount of vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating a patient with a neurological or psychiatric disease or disorder, ~~in a subject in need thereof comprising:~~

~~administering a vesicular monoamine transporter 2 (VMAT2) inhibitor to the subject in need thereof,~~

wherein the ~~subject~~ patient has severe renal impairment, and wherein the therapeutically effective amount is the same amount that would be administered to a patient with normal renal function.

~~6. The method of any one of claims 1 to 5, wherein the subject is not on chronic dialysis.~~

~~7. The method of any one of the preceding claims, wherein the amount of the VMAT2 inhibitor administered to the subject is not adjusted relative to a subject who has normal renal function.~~

~~8. The method of any one of claims 1 to 6, wherein the amount of the VMAT2 inhibitor administered to the subject is reduced relative to a subject who has normal renal impairment.~~

~~9. The method of any one of the preceding claims, further comprising determining the renal sufficiency level of the subject prior to administering the VMAT2 inhibitor.~~

~~10. The method of claim 9, wherein the Cockcroft-Gault equation is used to determine the level of renal sufficiency of the subject.~~

~~11. The method of claim 10, wherein the subject has a creatinine clearance rate of 15 to 29 mL/minute/1.73 m^2 using the Cockcroft-Gault equation.~~

~~12. The method of claim 9, wherein the subject's serum creatinine concentration is used to determine the level of renal sufficiency of the subject.~~

~~13. The method of claim 12, wherein the subject has an approximate serum creatinine concentration of:~~

~~less than 4.9 mg/dL for an 18-20 year old man,~~

~~less than 3.5 mg/dL for an 18-20 year old woman,~~

~~less than 4.5 mg/dL for a 21-30 year old man,~~

~~less than 3.2 mg/dL for a 21-30 year old woman,~~

~~less than 4.1 mg/dL for a 31-40 year old man,~~

~~less than 2.9 mg/dL for a 31-40 year old woman,~~

~~less than 2.7 mg/dL for a 41-50 year old woman,~~

~~less than 3.3 mg/dL for a 51-60 year old man,~~

~~less than 2.4 mg/dL for a 51-60 year old woman,~~

~~less than 3.0 mg/dL for a man over 60 years old, or~~

~~less than 2.0 mg/dL for a woman over 60 years old.~~

~~14. The method of any one of claims 1 to 4, wherein the VMAT2 inhibitor is administered to treat a neurological or psychiatric disease or disorder.~~

~~15. The method of any one of claims 5 to 14, wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder, mood disorder, bipolar disorder, schizophrenia, schizoaffective disorder, mania in mood disorder, depression in mood disorder, treatment-refractory obsessive compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, or chorea-acanthocytosis.~~

~~16. The method of claim 15, wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder.~~

~~17. The method of claim 16, wherein the hyperkinetic movement disorder is tardive dyskinesia.~~

~~18. The method of claim 16, wherein the hyperkinetic movement disorder is Tourette's syndrome.~~

~~19. The method of claim 16, wherein the hyperkinetic movement disorder is Huntington's disease.~~

~~20. The method of claim 16, wherein the hyperkinetic movement disorder is tics.~~

~~21. The method of claim 16, wherein the hyperkinetic movement disorder is chorea associated with Huntington's disease.~~

~~22. The method of claim 16, wherein the hyperkinetic movement disorder is ataxia, chorea, dystonia, Huntington's disease, myoclonus, restless leg syndrome, or tremors.~~

~~23. The method of any one of the preceding claims, wherein the VMAT2 inhibitor is administered orally.~~

~~24. The method of any one of the preceding claims, wherein the VMAT2 inhibitor is administered in the form of a tablet or capsule.~~

~~25. The method of any one of the preceding claims, wherein the VMAT2 inhibitor is administered with or without food.~~

~~26. The method of any one of the preceding claims, wherein the VMAT2 inhibitor is chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts and/or isotopic variants thereof.~~

~~27. The method of claim 26, wherein the VMAT2 inhibitor is chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof.~~

~~28. The method of claim 27, wherein the VMAT2 inhibitor is a tosylate salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester.~~

~~29. The method of claim 28, wherein the VMAT2 inhibitor is a ditosylate salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester.~~

~~30. The method of any one of claims 26 to 29, wherein the VMAT2 inhibitor is administered in an amount equivalent to between about 20 mg and about 160 mg of valbenazine free base.~~

~~31. The method of claim 30, wherein the VMAT2 inhibitor is administered in an amount equivalent to about 20 mg of valbenazine free base.~~

~~32. The method of claim 30, wherein the VMAT2 inhibitor is administered in an amount equivalent to about 40 mg of valbenazine free base.~~

~~33. The method of claim 30, wherein the VMAT2 inhibitor is administered in an amount equivalent to about 60 mg of valbenazine free base.~~

~~34. The method of claim 30, wherein the VMAT2 inhibitor is administered in an amount equivalent to about 80 mg of valbenazine free base.~~

~~35. The method of claim 30, wherein the VMAT2 inhibitor is administered in an amount equivalent to about 120 mg of valbenazine free base.~~

~~36. The method of any one of claims 1 to 29, wherein the VMAT2 inhibitor is administered for a first period of time in a first amount and then the amount is increased to a second amount.~~

~~37. The method of claim 36, wherein the first period of time is a week.~~

~~38. The method of claim 36 or 37, wherein the first amount is equivalent to about 40 mg of valbenazine free base.~~

~~39. The method of any one of claims 36 to 38, wherein the second amount is equivalent to about 80 mg of valbenazine free base.~~

~~40. The method of any one of claims 1 to 25, wherein the VMAT2 inhibitor is (+) α 3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof.~~

~~41. The method of claim 40, wherein the VMAT2 inhibitor is (+) α-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt thereof.~~

~~42. The method of claim 40, wherein the VMAT2 inhibitor is an isotopic variant that is (+)-α-3-isobutyl-9,10-di(methoxy-d_3)-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol or a pharmaceutically acceptable salt thereof.~~

~~43. A method of treating a patient with tardive dyskinesia, wherein the patient has severe renal impairment, comprising:~~

~~administering to the patient a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof, wherein the therapeutically effective amount is the same amount that is administered to a patient with normal renal function.~~

~~44. The method of claim 43, wherein the patient has a creatinine clearance rate of 15 to 29 mL/minute/1.73 m^2 using the Cockcroft-Gault equation.~~

~~45. The method of claim 43 or 44, wherein the patient has an approximate serum creatinine concentration of:~~

~~less than 4.9 mg/dL for an 18-20 year old man,~~

~~less than 3.5 mg/dL for an 18-20 year old woman,~~

~~less than 4.5 mg/dL for a 21-30 year old man,~~

~~less than 3.2 mg/dL for a 21-30 year old woman,~~

~~less than 4.1 mg/dL for a 31-40 year old man,~~

~~less than 2.9 mg/dL for a 31-40 year old woman,~~

~~less than 2.7 mg/dL for a 41-50 year old woman,~~

~~less than 3.3 mg/dL for a 51-60 year old man,~~

~~less than 2.4 mg/dL for a 51-60 year old woman,~~

~~less than 3.0 mg/dL for a man over 60 years old, or~~

~~less than 2.0 mg/dL for a woman over 60 years old.~~

~~46. The method of any one of claims 43 to 45, wherein the VMAT2 inhibitor is administered orally.~~

2. The use of claim 1, wherein the therapeutically effective amount is an amount equivalent to about 40 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.

3. The use of claim 1, wherein the therapeutically effective amount is an amount equivalent to about 60 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.

4. The use of claim 1, wherein the therapeutically effective amount is an amount equivalent to about 80 mg of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.

~~47.~~5. The ~~method~~use of any one of claims ~~43~~ 1 to ~~46~~4, wherein the VMAT2 inhibitor is to be administered in the form of a tablet or capsule.

~~48.~~6. The ~~method~~use of any one of claims ~~43~~ 1 to ~~47~~5, wherein the VMAT2 inhibitor is a salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester.

~~49.~~7. The ~~method~~use of ~~any one of claims 43 to 48~~claim 6, wherein the VMAT2 inhibitor is a ditosylate salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester.

~~50.~~8. The ~~method~~use of claim ~~49~~7, wherein the ditosylate salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester is in polymorphic ~~crystalline~~ Form I.

9. The use of any one of claims 1 to 8, wherein the patient has a creatinine clearance of < 30 mL/min.

~~51.~~10. The ~~method~~use of any one of claims ~~43~~ 1 to ~~50~~8, wherein the ~~patient has substantially similar~~ exposure~~s~~ of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and its active metabolite~~, ([+])~~-α−HTBZ~~,~~ in the patient with severe renal impairment is substantially similar~~compared~~ to the exposure~~s~~ of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and its active metabolite [+]-α-HTBZ in ~~a~~ the patient~~, who is administered the same amount of the VMAT2 inhibitor,~~ with normal renal function.

~~52.~~11. The ~~method~~use of claim ~~51~~10, wherein the exposure is measured by C_{max} ~~or $AUC_{0-\infty}$~~.

12. The use of claim 11, wherein the exposure is measured by $AUC_{0-\infty}$.

~~53. The method of any one of claims 43 to 52, wherein the therapeutically effective amount is an amount equivalent to about 40 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.~~

~~54. The method of any one of claims 43 to 52, wherein the therapeutically effective amount is an amount equivalent to about 60 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.~~

~~55. The method of any one of claims 43 to 52, wherein the therapeutically effective amount is an amount equivalent to about 80 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.~~

~~56. The method of any one of claims 43 to 52, wherein the therapeutically effective amount is a first amount once daily for one week, and subsequently a second amount once daily after one week.~~

~~57. The method of claim 56, wherein the first amount is an amount equivalent to about 40 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.~~

~~58. The method of claim 56, wherein the first amount is an amount equivalent to about 60 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.~~

~~59. The method of claim 56 or 57, wherein the second amount is an amount equivalent to about 60 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.~~

~~60. The method of any one of claims 56 to 58, wherein the second amount is an amount equivalent to about 80 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-~~

~~isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.~~

~~61.~~13. The ~~method~~use of any one of claims ~~43~~ 1 to ~~60~~8, wherein the VMAT 2 inhibitor does not undergo primary renal clearance.

14. The use of any one of claims 1 to 8, wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder.

15. The use of claim 14, wherein the hyperkinetic movement disorder is chorea.

16. The use of claim 14, wherein the hyperkinetic movement disorder is chorea associated with Huntington's disease.

17. The use of claim 14, wherein the hyperkinetic movement disorder is tardive dyskinesia.

~~62.~~18. ~~A method of~~ Use of a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating a patient with a neurological or psychiatric disease or disorder~~tardive dyskinesia~~, wherein~~comprising~~:

(a) ~~orally administering to the patient~~ a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof is to be orally administered to the patient~~,~~;

(b) ~~subsequently determining that~~ the patient is subsequently determined to have ~~has~~ severe renal impairment; and

(c) ~~continuing administering~~ administration of the same therapeutically effective amount of the VMAT2 inhibitor is to be continued.

~~63. The method of claim 62, wherein the patient has a creatinine clearance rate of 15 to 29 mL/minute/1.73 m^2 using the Cockcroft-Gault equation.~~

~~64.~~19. The ~~method~~use of claim ~~62 or 63~~18, wherein the VMAT2 inhibitor is to be administered in the form of a tablet or capsule.

~~65.~~20. The ~~method~~use of ~~any one of claims 62 to 64~~claim 18 or 19, wherein the VMAT2 inhibitor is a salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester.

~~66.~~21. The ~~method~~use of claim ~~65~~20, wherein the VMAT2 inhibitor is a ditosylate salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester.

22. The use of claim 21, wherein the ditosylate salt of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester is in polymorphic Form I.

~~67. The method of any one of claims 62 to 66, wherein the patient has substantially similar exposures of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and its active metabolite, (+)-α-HTBZ, in the patient compared to the exposures in a patient, who is administered the same amount of the VMAT2 inhibitor, with normal renal function.~~

~~68. The method of claim 67, wherein the exposure is measured by C_{max} or $AUC_{0-\infty}$.~~

~~69.~~23. The ~~method~~use of any one of claims ~~62~~ 18 to ~~68~~22, wherein the therapeutically effective amount is an amount equivalent to about 40 mg ~~as measured by~~of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.

~~70.~~24. The ~~method~~use of any one of claims ~~62~~ 18 to ~~68~~22, wherein the therapeutically effective amount is an amount equivalent to about 60 mg ~~as measured by~~of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.

~~71.~~25. The ~~method~~use of any one of claims ~~62~~ 18 to ~~68~~22, wherein the therapeutically effective amount is an amount equivalent to about 80 mg ~~as measured by~~of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base once daily.

26. The use of any one of claims 18 to 25, wherein the patient has a creatinine clearance of < 30 mL/min.

27. The use of any one of claims 18 to 26, wherein the exposure of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and its active metabolite [+]-α-HTBZ in the patient with severe renal impairment is substantially similar to the exposure of (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and its active metabolite [+]-α-HTBZ in a patient with normal renal function.

28. The use of claim 27, wherein the exposure is measured by C_{max}.

29. The use of claim 27, wherein the exposure is measured by $AUC_{0-\infty}$.

~~72. The method of any one of claims 62 to 68, wherein the therapeutically effective amount is a first amount once daily for one week, and subsequently a second amount once daily after one week.~~

~~73. The method of claim 72, wherein the first amount is an amount equivalent to about 40 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.~~

~~74. The method of claim 72, wherein the first amount is an amount equivalent to about 60 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.~~

~~75. The method of claim 72 or 73, wherein the second amount is an amount equivalent to about 60 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.~~

~~76. The method of claim 73 to 74, wherein the second amount is an amount equivalent to about 80 mg as measured by (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester free base.~~

~~77.~~30. The ~~method~~use of any one of claims ~~62~~ 18 to ~~76~~29, wherein the VMAT 2 inhibitor does not undergo primary renal clearance.

31. The use of any one of claims 18 to 30, wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder.

32. The use of claim 31, wherein the hyperkinetic movement disorder is chorea.

33. The use of claim 32, wherein the hyperkinetic movement disorder is chorea associated with Huntington's disease.

34. The use of claim 31, wherein the hyperkinetic movement disorder is tardive dyskinesia.

~~78. A pharmaceutical composition comprising a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester and pharmaceutically acceptable salts thereof for treating a patient with a neurological or psychiatric disease or disorder, wherein the patient has severe renal impairment.~~

~~79. The use of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from (S)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester in the manufacture of a medicament for treating a patient with a neurological or psychiatric disease or disorder, wherein the patient has severe renal impairment.~~