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 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 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 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 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 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 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 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 examples, tetrabenazine is chosen from the RR, SS, RS, and SR isomers of tetrabenazine, and mixtures thereof. In some examples, tetrabenazine is a mixture of the RR and SS isomers.

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

[0015] In some 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 examples, dihydrotetrabenazine is chosen from the RRR, SSS, SSRR, RSS, SSR, RRS, RSR, and SRS isomers of dihydrotetrabenazine, and mixtures thereof. In some 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 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. 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.

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.

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

6. The use of any one of claims 1 to 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.

7. The use of 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.

8. The use of claim 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 Form I.

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

10. The use of any one of claims 1 to 8, 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 the patient with normal renal function.

11. The use of claim 10, wherein the exposure is measured by $C_{max.}$

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

13. The use of any one of claims 1 to 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.

18. 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.

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

20. The use of 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.

21. The use of claim 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.

23. The use of any one of claims 18 to 22, 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.

24. The use of any one of claims 18 to 22, 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.

25. The use of any one of claims 18 to 22, 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.

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 $AUC_{0-\infty}$.

30. The use of any one of claims 18 to 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.