by CYP followed by a Roman or Arabic numeral, e.g., CYP2), and further divided into subfamilies (designated by a capital letter, e.g., CYP2D), which are comprised of those forms that are at least 55% related by their deduced amino acid sequences. Finally, the gene for each individual form of cytochrome P450 is assigned an Arabic number (e.g., CYP2D6).

[0007] Cytochrome P450 2D6 (CYP2D6), a member of the cytochrome P450 mixed-function oxidase system, is one of the most important enzymes involved in the metabolism of xenobiotics in the body. The CYP2D6 gene is highly polymorphic, with more than 70 allelic variants described.

[0008] There is a significant, unmet need for methods for administering a VMAT2 inhibitor, such as valbenazine or (+)-α-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-ol, or a pharmaceutically acceptable salt and/or isotopic variant thereof, to a patient in need thereof, wherein the patient is also being treated with another substance which may interact with the VMAT2 inhibitor, such as a CYP2D6 inhibitor. The present disclosure fulfills these and other needs, as evident in reference to the following disclosure.

SUMMARY

[0008a] In one aspect, the present disclosure provides use of a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder in a patient in need of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, wherein the patient is also being administered a strong cytochrome P450 2D6 (CYP2D6) inhibitor.

[0008b] In one aspect, the present disclosure provides use of a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder in a patient in need of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, wherein:

the patient is to be administered a therapeutically effective amount of the VMAT2 inhibitor,

the patient is to be subsequently determined to begin treatment with a strong cytochrome P450 2D6 (CYP2D6) inhibitor, and

administration of the therapeutically effective amount of the VMAT2 inhibitor to the patient is to be continued.

[0008c] In one aspect, the present disclosure provides use of a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder in a patient in need of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, wherein:

the patient is to be administered a therapeutically effective amount of the VMAT2 inhibitor,

the patient is to be subsequently determined to begin treatment with a strong cytochrome P450 2D6 (CYP2D6) inhibitor, and

a reduced amount of the VMAT2 inhibitor is to be administered to the patient.

[0009] Provided is a method of administering vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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 to a patient in need thereof, wherein the patient is also being administered a strong cytochrome P450 2D6 (CYP2D6) inhibitor, comprising: administering a therapeutically effective amount of the VMAT2 inhibitor to the patient.

[0010] Also provided is a method of administering a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, to a patient in need thereof, comprising: administering to the patient a therapeutically effective amount of the VMAT2 inhibitor, subsequently determining that the patient is to begin treatment with a strong cytochrome P450 2D6 (CYP2D6) inhibitor, and continuing administration of the therapeutically effective amount of the VMAT2 inhibitor to the patient.

[0011] Also provided is a method of administering a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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

CLAIMS:

1. Use of a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder in a patient in need of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, wherein the patient is also being administered a strong cytochrome P450 2D6 (CYP2D6) inhibitor.

2. The use of claim 1, wherein the patient is to be further monitored for one or more exposure-related adverse reactions.

3. The use of claim 1 or 2, wherein the amount of the VMAT2 inhibitor is to be further reduced based on the patient's ability to tolerate one or more exposure-related adverse reactions.

4. Use of a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder in a patient in need of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, wherein:

   the patient is to be administered a therapeutically effective amount of the VMAT2 inhibitor,

   the patient is to be subsequently determined to begin treatment with a strong cytochrome P450 2D6 (CYP2D6) inhibitor, and

   administration of the therapeutically effective amount of the VMAT2 inhibitor to the patient is to be continued.

5. Use of a therapeutically effective amount of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder in a patient in need of a vesicular monoamine transporter 2 (VMAT2) inhibitor chosen from valbenazine and (+)-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, wherein:

the patient is to be administered a therapeutically effective amount of the VMAT2 inhibitor,

the patient is to be subsequently determined to begin treatment with a strong cytochrome P450 2D6 (CYP2D6) inhibitor, and

a reduced amount of the VMAT2 inhibitor is to be administered to the patient.

6. The use of claim 4 or 5, wherein the patient is to be further monitored for one or more exposure-related adverse reactions.

7. The use of any one of claims 4 to 6, wherein the amount of the VMAT2 inhibitor is to be further reduced based on the patient's ability to tolerate one or more exposure-related adverse reactions.

8. The use of any one of claims 1 to 7, wherein the patient or a medical care worker is to be further informed that administration of the VMAT2 inhibitor to a patient who is also being administered a strong CYP2D6 inhibitor may result in increased exposure of (+)-α-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol.

9. The use of any one of claims 1 to 8, wherein the patient or a medical care worker is to be informed that administration of the VMAT2 inhibitor to a patient who is also being administered a strong CYP2D6 inhibitor may result in increased risk of one or more exposure-related adverse reactions.

10. The use of any one of claims 1 to 9, wherein the patient or a medical care worker is to be informed that co-administration of the VMAT2 inhibitor and a strong CYP2D6 inhibitor may prolong the patient's QT interval.

11. The use of any one of claims 2, 3, or 6 to 10, wherein the one or more exposure-related adverse reactions is chosen from somnolence, anticholinergic effects, balance disorders or falls, headache, akathisia, vomiting, nausea, arthralgia, QT prolongation, increase in blood glucose, increase in weight, respiratory infections, drooling, dyskinesia, extrapyramidal symptoms (non-

akathisia), anxiety, insomnia, increase in prolactin, increase in alkaline phosphatase, and increase in bilirubin.

12. The use of claim 11, wherein the one or more exposure-related adverse reactions is chosen from somnolence, anticholinergic effects, balance disorders or falls, headache, akathisia, vomiting, nausea, arthralgia, and QT prolongation.

13. The use of claim 12, wherein the one or more exposure-related adverse reactions is chosen from somnolence and QT prolongation.

14. The use of any one of claims 1 to 13, wherein the therapeutically effective amount is less than the amount that is to be administered to a patient who is not being administered a strong CYP2D6 inhibitor.

15. The use of any one of claims 1 to 13, wherein the therapeutically effective amount is the same amount as that is to be administered to a patient who is not being administered a strong CYP2D6 inhibitor.

16. The use of any one of claims 1 to 15, wherein the strong CYP2D6 inhibitor is chosen from bupropion, fluoxetine, metoclopramide, paroxetine, terbinafine, duloxetine, sertraline, and quinidine.

17. The use of claim 16, wherein the strong CYP2D6 inhibitor is chosen from fluoxetine, paroxetine, and quinidine.

18. The use of any one of claims 1 to 17, 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.

19. The use of claim 18, wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder.

20. The use of claim 19, wherein the hyperkinetic movement disorder is tardive dyskinesia.

21. The use of claim 19, wherein the hyperkinetic movement disorder is Tourette's syndrome.

22. The use of claim 19, wherein the hyperkinetic movement disorder is Huntington's disease.

23. The use of claim 19, wherein the hyperkinetic movement disorder is tics.

24. The use of claim 19, wherein the hyperkinetic movement disorder is chorea.

25. The use of claim 24, wherein the hyperkinetic movement disorder is chorea associated with Huntington's disease.

26. The use of any one of claims 1 to 25, wherein the VMAT2 inhibitor is to be administered orally.

27. The use of any one of claims 1 to 26, wherein the VMAT2 inhibitor is to be administered in the form of a tablet or capsule.

28. The use of any one of claims 1 to 27, wherein the VMAT2 inhibitor is to be administered with or without food.

29. The use of any one of claims 1 to 28, wherein the VMAT2 inhibitor is valbenazine or a pharmaceutically acceptable salt and/or isotopic variant thereof.

30. The use of claim 29, wherein the VMAT2 inhibitor is valbenazine or a pharmaceutically acceptable salt thereof.

31. The use of claim 30, wherein the VMAT2 inhibitor is a valbenazine tosylate salt.

32. The use of claim 31, wherein the VMAT2 inhibitor is a ditosylate salt of valbenazine.

33. The use of claim 29, wherein 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-d_3)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-yl ester or a pharmaceutically acceptable salt thereof.

34. The use of any one of claims 1 to 33, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to between 20 mg and 160 mg of valbenazine free base.

35. The use of claim 34, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to 20 mg of valbenazine free base.

36. The use of claim 34, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to 40 mg of valbenazine free base.

37. The use of claim 34, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to 60 mg of valbenazine free base.

38. The use of claim 34, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to 80 mg of valbenazine free base.

39. The use of claim 34, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to 120 mg of valbenazine free base.

40. The use of any one of claims 1 to 33, wherein the VMAT2 inhibitor is to be administered for a first period of time in a first amount and then the amount is to be increased to a second amount.

41. The use of claim 40, wherein the first period of time is a week.

42. The use of claim 40 or 41, wherein the first amount is equivalent to 40 mg of valbenazine free base.

43. The use of any one of claims 40 to 42, wherein the second amount is equivalent to 80 mg of valbenazine free base.

44. The use of any one of claims 1 to 33, wherein the VMAT2 inhibitor is to be administered in an amount sufficient to achieve a maximal blood plasma concentration (C_{max}) of (+)-α -DHTBZ of between 15 ng to 60 ng per mL plasma and a minimal blood plasma concentration (C_{min}) of (+)-α -DHTBZ of at least 15 ng per mL plasma over an 8 hour period.

45. The use of any one of claims 1 to 33, wherein the VMAT2 inhibitor is to be administered in an amount sufficient to achieve a maximal blood plasma concentration (C_{max}) of (+)-α -DHTBZ of between 15 ng to 60 ng per mL plasma and a minimal blood plasma concentration (C_{min}) of approximately between at least 33% -50% of the C_{max} over a 12 hour period.

46. The use of any one of claims 1 to 33, wherein the VMAT2 inhibitor is to be administered in an amount sufficient to achieve: (i) a therapeutic concentration range of 15 ng to 60 ng of (+)-α -DHTBZ per mL plasma; and (ii) a threshold concentration of at least 15 ng (+)-α -DHTBZ per mL plasma over a period of 8 hours to 24 hours.

47. The use of any one of claims 1 to 33, wherein the therapeutically effective amount of the VMAT2 inhibitor is 10-90% less than the amount that would be administered to a patient who is not also being administered a strong cytochrome P450 2D6 (CYP2D6) inhibitor.

48. The use of any one of claims 1 to 33, wherein the therapeutically effective amount of the VMAT2 inhibitor is 20-80% less than the amount that would be administered to a patient who is not also being administered a strong cytochrome P450 2D6 (CYP2D6) inhibitor.

49. The use of any one of claims 1 to 33, wherein the therapeutically effective amount of the VMAT2 inhibitor is 30-70% less than the amount that would be administered to a patient who is not also being administered a strong cytochrome P450 2D6 (CYP2D6) inhibitor.

50. The use of any one of claims 1 to 33, wherein the therapeutically effective amount of the VMAT2 inhibitor is 40-60% less than the amount that would be administered to a patient who is not also being administered a strong cytochrome P450 2D6 (CYP2D6) inhibitor.

51. The use of any one of claims 1 to 33, wherein the therapeutically effective amount of the VMAT2 inhibitor is 50% less than the amount that would be administered to a patient who is not also being administered a strong cytochrome P450 2D6 (CYP2D6) inhibitor.

52. The use of any one of claims 1 to 28, 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.

53. The use of claim 52, 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.

54. The use of claim 52, 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.