[0011] 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 a CYP2D6 poor metabolizer. The present disclosure fulfills these and other needs, as evident in reference to the following disclosure.

SUMMARY

[0011a] In one aspect, the present disclosure provides use of a therapeutically effective amount of 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, in the manufacture of a medicament for treating a patient in need of 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, wherein the patient is a cytochrome P450 2D6 (CYP2D6) poor metabolizer.

[0011b] In one aspect, the present disclosure provides use of a therapeutically effective amount of 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, in the manufacture of a medicament for treating a patient in need of 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, wherein:

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

the patient is to be subsequently determined a poor metabolizer of cytochrome P450 2D6 (CYP2D6), and

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

[0011c] In one aspect, the present disclosure provides use of a therapeutically effective amount of 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, in the manufacture of a medicament for treating a patient in need of 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, wherein:

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

the patient is to be subsequently determined a poor metabolizer of cytochrome P450 2D6 (CYP2D6), and

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

[0012] 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 wherein the patient is a cytochrome P450 2D6 (CYP2D6) poor metabolizer, comprising: administering a therapeutically effective amount of the VMAT2 inhibitor to the patient who is a CYP2D6 poor metabolizer.

[0013] 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 a poor metabolizer of cytochrome P450 2D6 (CYP2D6), and continuing administration of the therapeutically effective amount of the VMAT2 inhibitor to the patient.

[0014] 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 a poor metabolizer of cytochrome P450 2D6 (CYP2D6), and administering to the patient a reduced amount of the VMAT2 inhibitor.

[0015] 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.

CLAIMS:

1. Use of a therapeutically effective amount of 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, in the manufacture of a medicament for treating a patient in need of 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, wherein the patient is a cytochrome P450 2D6 (CYP2D6) poor metabolizer.

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 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, in the manufacture of a medicament for treating a patient in need of 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, wherein:

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

the patient is to be subsequently determined a poor metabolizer of cytochrome P450 2D6 (CYP2D6), 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 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, in the manufacture of a medicament for treating a patient in need of 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, wherein:

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

the patient is to be subsequently determined a poor metabolizer of cytochrome P450 2D6 (CYP2D6), 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 claim 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 a CYP2D6 poor metabolizer 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 further informed that administration of the VMAT2 inhibitor to a patient who is a CYP2D6 poor metabolizer 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 further informed that administration of the VMAT2 inhibitor to a patient who is a CYP2D6 poor metabolizer may prolong the patient's QT interval.

11. The use of claim 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 a CYP2D6 poor metabolizer.

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 a CYP2D6 poor metabolizer.

16. The use of any one of claims 1 to 15, wherein the patient has a CYP2D6 poor metabolizer genotype.

17. The use of claim 16, wherein the CYP2D6 poor metabolizer genotype is chosen from the CYP2D6G1846A genotype or the CYP2D6C100T genotype.

18. The use of claim 17, wherein the CYP2D6 poor metabolizer genotype is one of the CYP2D6G1846A (AA) genotype or the CYP2D6G1846A (AG) genotype.

19. The use of claim 18, wherein the CYP2D6 poor metabolizer genotype is the CYP2D6G1846A (AA) genotype.

20. The use of claim 17, wherein the CYP2D6 poor metabolizer genotype is one of the CYP2D6C100T (TT) genotype or the CYP2D6C100T (CT) genotype.

21. The use of claim 20, wherein the CYP2D6 poor metabolizer genotype is the CYP2D6C100T (TT) genotype.

22. The use of any one of claims 1 to 21, wherein the VMAT2 inhibitor is to be administered to the patient to treat a neurological or psychiatric disease or disorder.

23. The use of claim 22, 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.

24. The use of claim 23, wherein the neurological or psychiatric disease or disorder is a hyperkinetic movement disorder.

25. The use of claim 24, wherein the hyperkinetic movement disorder is tardive dyskinesia.

26. The use of claim 24, wherein the hyperkinetic movement disorder is Tourette's syndrome.

27. The use of claim 24, wherein the hyperkinetic movement disorder is Huntington's disease.

28. The use of claim 24, wherein the hyperkinetic movement disorder is tics.

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

30. The use of claim 24, wherein the hyperkinetic movement disorder is ataxia, chorea, dystonia, Huntington's disease, myoclonus, restless leg syndrome, or tremors.

31. The use of any one of claims 1 to 30, wherein the VMAT2 inhibitor is to be administered orally.

32. The use of any one of claims 1 to 31, wherein the VMAT2 inhibitor is to be administered in the form of a tablet or capsule.

33. The use of any one of claims 1 to 32, wherein the VMAT2 inhibitor is to be administered with or without food.

34. The use of any one of claims 1 to 33, wherein the VMAT2 inhibitor is valbenazine or a pharmaceutically acceptable salt and/or isotopic variant thereof.

35. The use of claim 34, wherein the VMAT2 inhibitor is valbenazine or a pharmaceutically acceptable salt thereof.

36. The use of claim 35, wherein the VMAT2 inhibitor is a valbenazine tosylate salt.

37. The use of claim 36, wherein the VMAT2 inhibitor is a ditosylate salt of valbenazine.

38. The use of claim 34, 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.

39. The use of any one of claims 1 to 38, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to between about 20 mg and about 160 mg of valbenazine free base.

40. The use of claim 39, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 20 mg of valbenazine free base.

41. The use of claim 39, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 40 mg of valbenazine free base.

42. The use of claim 39, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 60 mg of valbenazine free base.

43. The use of claim 39, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 80 mg of valbenazine free base.

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

45. The use of any one of claims 1 to 38, 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.

46. The use of claim 43, wherein the first period of time is a week.

47. The use of claim 43 or 44, wherein the first amount is equivalent to about 40 mg of valbenazine free base.

48. The use of any one of claims 43 to 45, wherein the second amount is equivalent to about 80 mg of valbenazine free base.

49. The use of any one of claims 1 to 38, 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 about 15 ng to about 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.

50. The use of any one of claims 1 to 38, 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 about 15 ng to about 60 ng per mL plasma and a minimal blood plasma concentration (C_{min}) of approximately between about at least 33% -50% of the C_{max} over a 12 hour period.

51. The use of any one of claims 1 to 38, wherein the VMAT2 inhibitor is to be administered in an amount sufficient to achieve: (i) a therapeutic concentration range of about 15 ng to about 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 about 8 hours to about 24 hours.

52. The use of any one of claims 1 to 38, 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 a CYP2D6 poor metabolizer.

53. The use of any one of claims 1 to 38, 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 a CYP2D6 poor metabolizer.

54. The use of any one of claims 1 to 38, 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 a CYP2D6 poor metabolizer.

55. The use of any one of claims 1 to 38, 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 a CYP2D6 poor metabolizer.

56. The use of any one of claims 1 to 38, wherein the therapeutically effective amount of the VMAT2 inhibitor is about 50% less than the amount that would be administered to a patient who is not a CYP2D6 poor metabolizer.

57. The use of any one of claims 1 to 33, 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.

58. The use of claim 57, 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.

59. The use of claim 57, 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.