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 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 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 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 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 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 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

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 administering to the patient a reduced amount of the VMAT2 inhibitor.

[0012] These and other aspects of the dislcosure 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 DESCRIPTION OF THE DRAWINGS

[0013] Fig. 1A: Mean (±SD) dose-normalized valbenazine concentrations were similar (P=0.249) with (3.375±2.037 ng/mL/mg) or without (3.683±2.360 ng/mL/mg) concomitant CYP2D6 inhibitors.

[0014] Fig. 1B. Mean dose-normalized [+]-α-HTBZ concentrations were also similar (P=0.571) with (0.534±0.321 ng/mL/mg) or without (0.513±0.326 ng/mL/mg) concomitant CYP2D6 inhibitors.

DETAILED DESCRIPTION

[0015] 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 structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to." Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0016] Reference throughout this specification to "one embodiment" or "an embodiment" or "some embodiments" or "a certain embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" or "in some embodiments" or "in a certain embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment.

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 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 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 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 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 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 VMAT2 inhibitor is to be administered to the patient to treat a neurological or psychiatric disease or disorder.

19. The use of claim 18, 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.

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

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

22. The use of claim 20, wherein the hyperkinetic movement disorder is Tourette's syndrome.

23. The use of claim 20, wherein the hyperkinetic movement disorder is Huntington's disease.

24. The use of claim 20, wherein the hyperkinetic movement disorder is tics.

25. The use of claim 20, wherein the hyperkinetic movement disorder is chorea associated with Huntington's disease.

26. The use of claim 20, wherein the hyperkinetic movement disorder is ataxia, chorea, dystonia, Huntington's disease, myoclonus, restless leg syndrome, or tremors.

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

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

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

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

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

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

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

34. The use of claim 30, 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.

35. The use of any one of claims 1 to 34, 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.

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

37. The use of claim 35, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 40 mg of valbenazine free base.

38. The use of claim 35, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 60 mg of valbenazine free base.

39. The use of claim 35, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 80 mg of valbenazine free base.

40. The use of claim 35, wherein the VMAT2 inhibitor is to be administered in an amount equivalent to about 120 mg of valbenazine free base.

41. The use of any one of claims 1 to 34, 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.

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

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

44. The use of any one of claims 41 to 43, wherein the second amount is equivalent to about 80 mg of valbenazine free base.

45. The use of any one of claims 1 to 34, 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.

46. The use of any one of claims 1 to 34, 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.

47. The use of any one of claims 1 to 34, 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.

48. The use of any one of claims 1 to 34, 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.

49. The use of any one of claims 1 to 34, 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.

50. The use of any one of claims 1 to 34, 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.

51. The use of any one of claims 1 to 34, 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.

52. The use of any one of claims 1 to 34, 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 also being administered a strong cytochrome P450 2D6 (CYP2D6) inhibitor.

53. The use of any one of claims 1 to 29, 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.

54. The use of claim 53, 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.

55. The use of claim 53, 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.