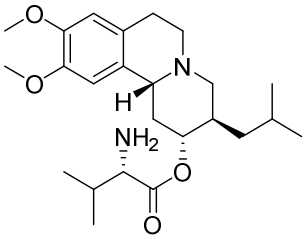
METHODS FOR THE ADMINISTRATION OF CERTAIN VMAT2 INHIBITORS

[0001] Dysregulation of dopaminergic systems is integral to several central nervous system (CNS) disorders, including neurological and psychiatric diseases and disorders. These neurological and psychiatric diseases and disorders include hyperkinetic movement disorders, and conditions such as schizophrenia and mood disorders. The transporter protein vesicular monoamine transporter-2 (VMAT2) plays an important role in presynaptic dopamine release and regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release.

[0002] Despite the advances that have been made in this field, there remains a need for new therapeutic products useful to treatment of neurological and psychiatric diseases and disorders and other related diseases or conditions described herein. One such agent is valbenazine, which has the following chemical structure:



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[0003] A formulation of the VMAT2 inhibitor, valbenazine:4-toluenesulfonate (1:2) (referred to herein as "valbenazine ditosylate" or “ditosylate salt of valbenazine”) has been previously reported in the FDA approved drug label INGREZZA® (hereafter referred to as INGREZZA). INGREZZA was approved in the United States on 11 April 2017 for the treatment of adults with tardive dyskinesia (TD).

[0004] There is a significant, unmet need for methods of administering a VMAT2 inhibitor, such as valbenazine, or a pharmaceutically acceptable salt and/or isotopic variant thereof, to a patient in need thereof with reduced adverse events, such as parkinsonism. The present disclosure fulfills these and other needs, as evident in reference to the following disclosure.

SUMMARY

[0004a] In one aspect, the present disclosure refers to 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 and a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient with a neurological or psychiatric disease or disorder, wherein:

a therapeutically effective amount of the 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 a pharmaceutically acceptable salt thereof is to be orally administered to the patient for a period of up to two weeks;

the patient is to be monitored for the presence or absence of one or more clinically significant parkinson-like signs or symptoms;

if the patient experiences one or more clinically significant parkinson-like signs or symptoms during the period of up to two weeks, a reduced amount of the VMAT2 inhibitor is to be administered to the patient or administration of the VMAT2 inhibitor to the patient is to be discontinued; and

if the patient does not experience one or more clinically significant parkinson-like signs or symptoms during the period of up to two weeks, administration of the VMAT2 inhibitor to the patient is to be continued at the same therapeutically effective amount or administration of the VMAT2 inhibitor is to be initiated at an increased amount.

[0005] Provided is a method of administering a vesicular monoamine transport 2 (VMAT2) inhibitor to a patient in need thereof, comprising:

administering a therapeutically effective amount of the VMAT2 inhibitor to the patient;

monitoring the patient for one or more clinically significant parkinson-like signs or symptoms; and

administering a reduced amount of the VMAT2 inhibitor to the patient, if the patient experiences one or more clinically significant parkinson-like signs or symptoms,

wherein if the VMAT2 inhibitor is tetrabenazine or deutrabenazine, the VMAT2 inhibitor is being administered to treat a disease or disorder other than Huntington's Disease.

[0006] Also provided is a method of administering a vesicular monoamine transport 2 (VMAT2) inhibitor to a patient in need thereof, wherein the patient is experiencing one or more clinically significant parkinson-like signs or symptoms, comprising administering a reduced amount of the VMAT2 inhibitor to the patient, wherein the reduced amount of the VMAT2 administered is less than the therapeutically effective amount that would be administered to a patient who is not experiencing one or more clinically significant parkinson-like signs or symptoms, wherein if the VMAT2 inhibitor is tetrabenazine or deutrabenazine, the VMAT2 inhibitor is being administered to treat a disease or disorder other than Huntington's Disease.

[0007] In some examples, the method further comprising discontinuing the administration of the VMAT2 inhibitor based on the patient's ability to tolerate one or more clinically significant parkinson-like signs and symptoms.

[0008] Also provided is a method of administering a vesicular monoamine transport 2 (VMAT2) inhibitor to a patient in need thereof, comprising:

administering a therapeutically effective amount of the VMAT2 inhibitor to the patient;

monitoring the patient for one or more clinically significant parkinson-like signs or symptoms; and

discontinuing the administration of the VMAT2 inhibitor to the patient if the patient experiences one or more clinically significant parkinson-like signs or symptoms,

wherein if the VMAT2 inhibitor is tetrabenazine or deutrabenazine, the VMAT2 inhibitor is being administered to treat a disease or disorder other than Huntington's Disease.

[0009] In some examples, the VMAT2 inhibitor is chosen from valbenazine, or a pharmaceutically acceptable salt and/or isotopic variant thereof. In some examples, the VMAT2 inhibitor is valbenazine, or a pharmaceutically acceptable salt thereof. In some examples, the VMAT2 inhibitor is a valbenazine tosylate salt. In some examples, the VMAT2 inhibitor is a valbenazine tosylate salt. In some examples, the VMAT2 inhibitor is

a ditosylate salt of valbenazine. In some further examples, the ditosylate salt of valbenazine is substantially crystalline.

[0010] 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.

[0011] 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.

[0012] In some examples, the VMAT2 inhibitor is deutetrabenazine.

[0013] 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.

[0014] Also provided is a method of treating a patient with a hyperkinetic movement disorder, such as tardive dyskinesia, comprising:

orally administering to the patient for a period of up to two weeks a therapeutically effective amount of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and pharmaceutically acceptable salts thereof; and

if the patient does not experience one or more clinically significant parkinson-like signs or symptoms during the period of up to two weeks, continuing administration of the VMAT2 inhibitor at the therapeutically effective dose or initiating administration of the VMAT2 inhibitor at an increased dose.

[0015] Also provided is a method of treating a patient with a hyperkinetic movement disorder, such as tardive dyskinesia, comprising:

orally administering to the patient for a period of up to two weeks a therapeutically effective amount of a vesicular monoamine transport 2 (VMAT2) inhibitor chosen from valbenazine and pharmaceutically acceptable salts thereof; and

if the patient experiences one or more clinically significant parkinson-like signs or symptoms during the period of up to two weeks, discontinuing administration of the VMAT2 inhibitor at the therapeutically effective dose or initiating administration of the VMAT2 inhibitor at a reduced dose.

[0016] In some examples, the method further comprises selecting a patient for continued treatment with the VMAT2 inhibitor if the patient has not experienced one or more clinically significant parkinson-like signs or symptoms within the first two weeks after starting or increasing the dose of the VMAT2 inhibitor administered to the patient.

[0017] 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.

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 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.

[0019] 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

What is claimed is:

1. 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 and a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient with a neurological or psychiatric disease or disorder, wherein:

a therapeutically effective amount of the 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 a pharmaceutically acceptable salt thereof is to be orally administered to the patient for a period of up to two weeks;

the patient is to be monitored for the presence or absence of one or more clinically significant parkinson-like signs or symptoms;

if the patient experiences one or more clinically significant parkinson-like signs or symptoms during the period of up to two weeks, a reduced amount of the VMAT2 inhibitor is to be administered to the patient or administration of the VMAT2 inhibitor to the patient is to be discontinued; and

if the patient does not experience one or more clinically significant parkinson-like signs or symptoms during the period of up to two weeks, administration of the VMAT2 inhibitor to the patient is to be continued at the same therapeutically effective amount or administration of the VMAT2 inhibitor is to be initiated at an increased amount.

2. The use of claim 1, wherein the VMAT2 inhibitor is a pharmaceutically acceptable 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.

3. The use of claim 1 or 2, wherein the VMAT2 inhibitor is (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 ditosylate.

4. The use of any one of claims 1 to 3, wherein the therapeutically effective amount is a first amount for one week and the amount is to be increased to a second amount after one week.

5. The use of claim 4, wherein the first 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.

6. The use of claim 4 or 5, wherein the second 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.

7. The use of claim 4 or 5, wherein the second 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.

8. The use of any one of claims 1 to 7, wherein the reduced 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.

9. The use of any one of claims 1 to 5 and 7, wherein the reduced 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.

10. The use of any one of claims 1 to 9, wherein the one or more clinically significant parkinson-like signs or symptoms is chosen from falls, gait disturbances, tremor, drooling and hypokinesia.

11. The use of any one of claims 1 to 9, wherein the one or more clinically significant parkinson-like signs or symptoms is chosen from difficulty moving or loss of ability to move muscles voluntarily, tremor, gait disturbances and drooling.

12. The use of any one of claims 1 to 9, wherein the one or more clinically significant parkinson-like signs or symptoms is tremor.

13. The use of any one of claims 1 to 9, wherein the one or more clinically significant parkinson-like signs or symptoms is drooling.

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