SUMMARY

In one example, this disclosure relates to use of a VMAT2 inhibitor for treating mania in mood disorders. Provided herein are new methods of treating mania in mood disorders, *e.g.*, bipolar disorder, in subjects in need thereof by administering a VMAT2 inhibitor. The present disclosure provides the following examples. These and additional examples are described in greater detail herein.

Example 1. A method for treating mania in a mood disorder in a subject comprising administering to the subject a selective VMAT2 inhibitor.

In one aspect, the present disclosure refers to use of a VMAT2 inhibitor in the manufacture of a medicament for the treatment of a neurological disorder, wherein the neurological disorder is treatment-refractory obsessive-compulsive disorder (OCD), or mania in a mood disorder.

Example 2. A method for treating mania in a mood disorder in a subject comprising administering to the subject a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

In another aspect, the present disclosure refers to use of a VMAT2 inhibitor selected from: 3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one; (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ); (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof, in the manufacture of a medicament for the treatment of a neurological disorder, wherein the neurological disorder is treatment-refractory obsessive-compulsive disorder (OCD), or mania in a mood disorder.

Example 3. The method of example 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 4. The method of example 3, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 5. The method of any one of examples 1-4, wherein the mood disorder is bipolar disorder.

Example 6. The method of example 5, wherein the mania in the mood disorder is hypomania or severe mania.

Example 7. The method of any one of examples 1-6, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 8. The method of any one of examples 1-7, wherein the VMAT2 inhibitor is administered orally.

Example 9. The method of example 8, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 10. A pharmaceutical composition for use in treating mania in a mood disorder, said composition comprising a pharmaceutically acceptable excipient and a selective VMAT2 inhibitor.

Example 11. A pharmaceutical composition for use in treating mania in a mood disorder, said composition comprising a pharmaceutically acceptable excipient and a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

In another aspect, the present disclosure refers to use of a VMAT2 inhibitor selected from: (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ); and (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; or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof, in the manufacture of a medicament for the treatment of a neurological disorder, wherein the neurological disorder is depression in a mood disorder.

Example 12. The pharmaceutical composition of example 10 or 11, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 13. The pharmaceutical composition of example 12, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-

2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 14. The pharmaceutical composition of any one of examples 11-13, wherein the mood disorder is bipolar disorder.

Example 15. The pharmaceutical composition of example 14, wherein the mania in the mood disorder is hypomania or severe mania.

Example 16. The pharmaceutical composition of any one of examples 11-15, wherein the pharmaceutical composition is formulated as a dosage form having about 5 mg to about 100 mg of the VMAT2 inhibitor.

Example 17. The pharmaceutical composition of any one of examples 11-16, wherein the pharmaceutical composition is formulated for oral administration.

Example 18. The pharmaceutical composition of example 17, wherein the pharmaceutical composition is formulated as a tablet or capsule.

In another example, this disclosure relates to use of a VMAT2 inhibitor for treating symptoms associated with treatment-refractory OCD. Provided herein are new methods of treating treatment refractory OCD in subjects in need thereof by administering a VMAT2 inhibitor. The present disclosure provides the following embodiments. These and additional examples are described in greater detail herein.

Example 19. A method for treating treatment-refractory obsessive-compulsive disorder (OCD) in a subject comprising administering to the subject a selective VMAT2 inhibitor.

Example 20. A method for treating treatment-refractory OCD in a subject comprising administering to the subject a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-

Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 21. The method of example 19 or 20, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 22. The method of example 21, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 23. The method of any one of examples 19-22, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 24. The method of any one of examples19-23, wherein the VMAT2 inhibitor is administered orally.

Example 25. The method of example 24, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 26. The method of any one of examples 19-25, wherein the frequency or severity of cleaning, hoarding, a counting ritual, a checking ritual, a line-crossing, a prayer ritual, a hand washing ritual, following a strict routine, orderliness, requesting reassurance, or a combination thereof is reduced.

Example 27. A pharmaceutical composition for use in treating treatment-refractory OCD, said composition comprising a pharmaceutically acceptable excipient and a selective VMAT2 inhibitor.

Example 28. A pharmaceutical composition for use in treating treatment-refractory OCD, said composition comprising a pharmaceutically acceptable excipient and a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one);

(2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant thereof , a pharmaceutically acceptable salt, or polymorph thereof.

Example 29. The pharmaceutical composition of example 27 or 28, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 30. The pharmaceutical composition of example 28 or 29, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 31. The pharmaceutical composition of any one of examples 27-30, wherein the pharmaceutical composition is formulated as a dosage form having about 10 mg to about 80 mg of the VMAT2 inhibitor.

Example 32. The pharmaceutical composition of any one of examples 27-31, wherein the pharmaceutical composition is formulated for oral administration.

Example 33. The pharmaceutical composition of example 32, wherein the pharmaceutical composition is formulated as a solution, tablet or capsule.

Example 34. The pharmaceutical composition of any one of examples 27-33, wherein the frequency or severity of cleaning, hoarding, a counting ritual, a checking ritual, a line-crossing, a prayer ritual, a hand washing ritual, following a strict routine, orderliness, requesting reassurance, or a combination thereof is reduced.

In another example, this disclosure relates to use of a VMAT2 inhibitor for treating a neurological dysfunction associated with Lesch-Nyhan syndrome. Provided herein are new methods of treating Lesch-Nyhan syndrome in subjects in need thereof by administering a VMAT2 inhibitor. The present disclosure provides the following examples. These and additional examples are described in greater detail herein.

Example 35. A method for treating a neurological dysfunction associated with Lesch-Nyhan syndrome in a subject comprising administering to the subject a selective VMAT2 inhibitor.

Example 36. A method for treating a neurological dysfunction associated with Lesch-Nyhan syndrome in a subject comprising administering to the subject a VMAT2 inhibitor selected from: (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 37. The method of example 35 or 36, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 38. The method of example 37, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 39. The method of any one of examples 35-38, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 40. The method of any one of examples 35-39, wherein the VMAT2 inhibitor is administered orally.

Example 41. The method of example 40, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 42. The method of any one of examples 35-41, wherein the neurological dysfunction associated with Lesch-Nyhan syndrome is one or more of self-injury, dystonia, spasticity, chorea, choreoathetosis, opisthotonos, ballismus, hyperreflexia, and extensor plantar reflex.

Example 43. A pharmaceutical composition for use in treating a neurological dysfunction associated with Lesch-Nyhan syndrome, said composition comprising a pharmaceutically acceptable excipient and a selective VMAT2 inhibitor.

Example 44. A pharmaceutical composition for use in treating a neurological dysfunction associated with Lesch-Nyhan syndrome, said composition comprising a pharmaceutically acceptable excipient and a VMAT2 inhibitor selected from: (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or polymorph thereof.

Example 45. The pharmaceutical composition of example 43 or 44, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 46. The pharmaceutical composition of example 45, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 47. The pharmaceutical composition of any one of examples 43-46, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 48. The pharmaceutical composition of any one of examples 43-47, wherein the VMAT2 inhibitor is administered orally.

Example 49. The pharmaceutical composition of example 48, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 50. The pharmaceutical composition of examples 43-49, wherein the neurological dysfunction associated with Lesch-Nyhan syndrome is one or more of self-injury, dystonia, spasticity, chorea, choreoathetosis, opisthotonos, ballismus, hyperreflexia, and extensor plantar reflex.

In yet another example, this disclosure relates to use of a VMAT2 inhibitor for treating agitation in Alzheimer's disease (also referred to herein as agitation associated with Alzheimer's disease). Provided herein are new methods of treating agitation in a subject who has Alzheimer's disease by administering a VMAT2 inhibitor. The present disclosure provides the following examples.

Example 51. A method for treating agitation in a subject who has Alzheimer's disease comprising administering to the subject a VMAT2 inhibitor.

Example 52. The method of example 51, wherein the VMAT2 inhibitor is a selective VMAT2 inhibitor.

Example 53. The method of example 51 or 52, wherein the VMAT2 inhibitor is selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof;.3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-

a]isoquinolin-2-one (d_6-TBZ) ; or an isotopic variant, a pharmaceutically acceptable salt, an isotopic variant, thereof.

Example 54. The method of example 52 or 53, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 55. The method of example 54, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 56. The method of any one of examples 51-55, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 57. The method of any one of examples 51-56, wherein the VMAT2 inhibitor is administered orally.

Example 58. The method of example 67, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 59. The method of any one of examples 51-58, wherein the agitation associated with Alzheimer's disease is one or more of anxiety, irritability, pacing, excessive fidgeting, repetitive behaviors, abnormal vocalization, and motor restlessness.

Example 60. A pharmaceutical composition for use in treating agitation in Alzheimer's disease, said composition comprising a pharmaceutically acceptable excipient and a VMAT2 inhibitor.

Example 61. A pharmaceutical composition for use of example 60 in treating agitation associated with Alzheimer's, said composition comprising a pharmaceutically acceptable excipient and a selective VMAT2 inhibitor.

Example 62. The pharmaceutical composition of example 60 or 61, wherein the VMAT2 inhibitor is selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one);

(2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methano, or a precursor thereof l; 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 63. The pharmaceutical composition of example 61 or 62, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 64. The pharmaceutical composition of example 63, wherein the VMAT 2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 65. The pharmaceutical composition of any one of examples 60-64, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 66. The pharmaceutical composition of any one of examples 60-65, wherein the VMAT2 inhibitor is administered orally.

Example 67. The pharmaceutical composition of example 66, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 68. The pharmaceutical composition of any one of examples 60-67, wherein the agitation associated with Alzheimer's disease is one or more of anxiety, irritability, pacing, excessive fidgeting, repetitive behaviors, abnormal vocalization, and motor restlessness.

In another example, this disclosure relates to use of a VMAT2 inhibitor for treating Fragile X syndrome and Fragile X-associated tremor-ataxia syndrome. Provided herein are methods of treating Fragile X syndrome (FXS) and Fragile X-

associated tremor-ataxia syndrome (FXTAS) in subjects in need thereof by administering a VMAT2 inhibitor. The present disclosure provides the following examples.

Example 69. A method for treating Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome in a subject comprising administering to the subject a selective VMAT2 inhibitor.

Example 70. A method for treating Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome in a subject comprising administering to the subject a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 71. The method of example 69 or 70, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 72. The method of example 71, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 73. The method of any one of examples 69-72, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 74. The method of any one of examples 69-73, wherein the VMAT2 inhibitor is administered orally.

Example 75. The method of example 74, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 76. The method of any one of examples 70-75, wherein one or more of anxiety, an attentional deficit, a hyperactive behavior (*e.g.,* fidgeting or impulsive actions), an autistic type behavior (*e.g.,* a repetitive behavior), seizures, ataxia, intention tremor (trembling or shaking of a limb when the affected individual is trying to perform a voluntary movement), parkinsonism, resting tremor, rigidity, bradykinesia, reduced sensation, numbness, pain, and muscle weakness is reduced.

Example 77. A pharmaceutical composition for use in treating Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, said composition comprising a pharmaceutically acceptable excipient and a selective VMAT2 inhibitor.

Example 78. A pharmaceutical composition for use in treating Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, said composition comprising a pharmaceutically acceptable excipient and a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or polymorph thereof.

Example 79. The pharmaceutical composition of example 77 or 78, 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 or an isotopic variant, a pharmaceutically acceptable salt, or polymorph thereof.

Example 80. The pharmaceutical composition of example 79, wherein the VMAT 2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 81. The pharmaceutical composition of any one of examples 77-80, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 82. The pharmaceutical composition of any one of examples 77-81, wherein the VMAT2 inhibitor is administered orally.

Example 83. The pharmaceutical composition of example82, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 84. The pharmaceutical composition of any one of examples 77-83, wherein the one or more of anxiety, an attentional deficit, a hyperactive behavior (*e.g.,* fidgeting or impulsive actions), an autistic type behavior (*e.g.,* a repetitive behavior), seizures, ataxia, intention tremor (trembling or shaking of a limb when the affected individual is trying to perform a voluntary movement), parkinsonism, resting tremor, rigidity, bradykinesia, reduced sensation, numbness, pain, and muscle weakness is reduced.

In another example, this disclosure relates to use of a VMAT2 inhibitor for treating autism spectrum disorder. Provided herein are methods of treating autism spectrum disorder in subjects in need thereof by administering a VMAT2 inhibitor. The present disclosure provides the following examples.

Example 85. A method for treating autism spectrum disorder (ASD) in a subject comprising administering to the subject a VMAT2 inhibitor.

Example 86. The method of example 85, wherein the VMAT2 inhibitor is a selective VMAT2 inhibitor.

Example 87. The method of example 85 or 86, wherein the VMAT2 inhibitor is selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol

(R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or polymorph thereof..

Example 88. The method of example 86 or 87, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 89. The method of example 88, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 90. The method of any one of examples 85-89, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 91. The method of any one of examples 85-90, wherein the VMAT2 inhibitor is administered orally.

Example 92. The method of example 91, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 93. The method of any one of examples 85-92, wherein one or more of hyperactivity, inability to focus, depression, anxiety, obsessive-compulsive behavior, seizures, repetitive movements, or self-injury is reduced.

Example 94. A pharmaceutical composition for use in treating autism spectrum disorder (ASD), said composition comprising a VMAT2 inhibitor and a pharmaceutically acceptable excipient.

Example 95. The pharmaceutical composition of example 94, wherein the VMAT2 inhibitor is a selective VMAT2 inhibitor.

Example 96. The pharmaceutical composition of example 94 or 95, wherein the VMAT2 inhibitor is selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymoroph thereof.

Example 97. The pharmaceutical composition of example 95 or 96, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 98. The pharmaceutical composition of example 97, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 99. The pharmaceutical composition of any one of examples 94-98, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 100. The pharmaceutical composition of any one of examples 94-99, wherein the VMAT2 inhibitor is administered orally.

Example 101. The pharmaceutical composition of examplet 100, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 102. The pharmaceutical composition of any one of examples 94-101, wherein one or more of hyperactivity, inability to focus, depression, anxiety, obsessive-compulsive behavior, seizures, involuntary movements, repetitive movements, stereotypies or self-injury is reduced.

In another example, this disclosure relates to use of a VMAT2 inhibitor for treating depression in mood disorders. Provided herein are new methods of treating depression in mood disorders in subjects in need thereof by administering a VMAT2 inhibitor. The present disclosure provides the following examples. These and additional examples are described in greater detail herein.

Example 103. A method for treating depression in a mood disorder in a subject comprising administering to the subject a selective VMAT2 inhibitor.

Example 104. A method for treating depression in a mood disorder in a subject comprising administering to the subject a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 105. The method of example 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 106. The method of example 105, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 107. The method of any one of examples 103-106, wherein the mood disorder is bipolar disorder.

Example 108. The method of any one of examples 103-106, wherein the mood disorder is major depressive disorder.

Example 109. The method of any one of examples 103-108, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 110. The method of any one of examples 103-109, wherein the VMAT2 inhibitor is administered orally.

Example 111. The method of example 110, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 112. A pharmaceutical composition for use in treating depression in a mood disorder, said composition comprising a pharmaceutically acceptable excipient and a selective VMAT2 inhibitor.

Example 113. A pharmaceutical composition for use in treating depression in a mood disorder, said composition comprising a pharmaceutically acceptable excipient and a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 114. The pharmaceutical composition of example 112 or 113, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 115. The pharmaceutical composition of example 114, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-

2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 116. The pharmaceutical composition of any one of examples 112-115, wherein the mood disorder is bipolar disorder.

Example 117. The pharmaceutical composition of example 116, wherein the mood disorder is major depressive disorder.

Example 118. The pharmaceutical composition of any one of examples 112-117, wherein the pharmaceutical composition is formulated as a dosage form having about 5 mg to about 100 mg of the VMAT2 inhibitor.

Example 119. The pharmaceutical composition of any one of examples 110-116, wherein the pharmaceutical composition is formulated for oral administration.

Example 120. The pharmaceutical composition of example 119, wherein the pharmaceutical composition is formulated as a tablet or capsule.

In another example, this disclosure relates to use of a VMAT2 inhibitor for treating chorea-acanthocytosis. Provided herein are new methods of treating chorea-acanthocytosis in subjects in need thereof by administering a VMAT2 inhibitor. The present disclosure provides the following examples. These and additional examples are described in greater detail herein.

Example 121. A method for treating chorea-acanthocytosis in a subject comprising administering to the subject a selective VMAT2 inhibitor.

Example 122. A method for treating chorea-acanthocytosis in a subject comprising administering to the subject a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-

hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 123. The method of example 121 or 122, for treating lingual dyskinesia in chorea-acanthocytosis.

Example 124. The method of any one of examples 121-123, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 125. The method of example 124, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 126. The method of any one of examples 121-125, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 127. The method of any one of examples 121-126, wherein the VMAT2 inhibitor is administered orally.

Example 128. The method of example 127, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 129. A pharmaceutical composition for use in treating chorea-acanthocytosis, said composition comprising a pharmaceutically acceptable excipient and a selective VMAT2 inhibitor.

Example 130. A pharmaceutical composition for use in treating chorea-acanthocytosis, said composition comprising a pharmaceutically acceptable excipient and a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-

methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 131. The pharmaceutical composition of example 129 or 130, for treating lingual dyskinesia in chorea-acanthocytosis.

Example 132. The pharmaceutical composition of any one of examples 127-129, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 133. The pharmaceutical composition of example 130, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 134. The pharmaceutical composition of any one of examples 129-133, wherein the pharmaceutical composition is formulated as a dosage form having about 5 mg to about 100 mg of the VMAT2 inhibitor.

Example 135. The pharmaceutical composition of any one of examples 129-134, wherein the pharmaceutical composition is formulated for oral administration.

Example 136. The pharmaceutical composition of example 135, wherein the pharmaceutical composition is formulated as a tablet or capsule.

In yet another example, this disclosure relates to use of a VMAT2 inhibitor for treating Rett syndrome. Provided herein are new methods of treating Rett syndrome in subjects in need thereof by administering a VMAT2 inhibitor. The present disclosure provides the following examples. These and additional examples are described in greater detail herein.

Example 137. A method for treating Rett syndrome in a subject comprising administering to the subject a selective VMAT2 inhibitor.

Example 138. A method for treating Rett syndrome in a subject comprising administering to the subject a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 139. The method of example 137 or 138, for treating apraxia in Rett syndrome.

Example 140. The method of any one of examples 137-139, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 141. The method of example 140, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 142. The method of any one of examples 137-141, wherein the VMAT2 inhibitor is administered at a daily dose of about 5 mg to about 100 mg.

Example 143. The method of any one of examples 137-142, wherein the VMAT2 inhibitor is administered orally.

Example 144. The method of example 143, wherein the VMAT2 inhibitor is administered as a tablet or capsule.

Example 145. A pharmaceutical composition for use in treating Rett syndrome, said composition comprising a pharmaceutically acceptable excipient and a selective VMAT2 inhibitor.

Example 146. A pharmaceutical composition for use in treating Rett syndrome, said composition comprising a pharmaceutically acceptable excipient and a VMAT2 inhibitor selected from: tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one); (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof; (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; [(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol, or a precursor thereof; and 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 147. The pharmaceutical composition of example 145 or 146, for treating apraxia in Rett syndrome.

Example 148. The pharmaceutical composition of any one of examples 145-146, 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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

Example 149. The pharmaceutical composition of example 148, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

Example 150. The pharmaceutical composition of any one of example 145-149, wherein the pharmaceutical composition is formulated as a dosage form having about 5 mg to about 100 mg of the VMAT2 inhibitor.

Example 151. The pharmaceutical composition of any one of examples 145-150, wherein the pharmaceutical composition is formulated for oral administration.

Example 152. The pharmaceutical composition of example 151, wherein the pharmaceutical composition is formulated as a tablet or capsule.

In an example of the compositions and methods described above and herein, the VMAT2 inhibitor is tetrabenazine (3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one) or a pharmaceutically acceptable salt thereof. In another specific example, the VMAT2 inhibitor is (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a precursor thereof or a pharmaceutically acceptable salt thereof. In yet another specific example, 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. In another specific example 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, *e.g.*, ditosylate salt. In another example, the VMAT2 inhibitor is deuterated tetrabenazine, particularly 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ) or a pharmaceutically acceptable salt thereof. In another example, the VMAT2 inhibitor is [(2R,3S,11bR)-9,10-dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol or a precursor thereof or a pharmaceutically acceptable salt thereof.

In still other particular examples, the methods and uses described herein comprise administering a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a VMAT2 inhibitor.

These and other examples of the disclosure will be apparent upon reference to the following detailed description. To this end, various references are set forth herein that describe in more detail certain background information, procedures, compounds and/or compositions, and are each hereby incorporated by reference in their entirety.

CLAIMS

I claim the following:

1. Use of a VMAT2 inhibitor in the manufacture of a medicament for the treatment of a neurological disorder, wherein the neurological disorder is treatment-refractory obsessive-compulsive disorder (OCD), or mania in a mood disorder.

2. Use of a VMAT2 inhibitor selected from:

3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one;

(2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ);

(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;

[(2R,3S,11bR)-9,10-Dimethoxy-3-(2-methylpropyl)-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinolin-2-yl]methanol; and

3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ); or

an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof,

in the manufacture of a medicament for the treatment of a neurological disorder, wherein the neurological disorder is treatment-refractory obsessive-compulsive disorder (OCD), or mania in a mood disorder.

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 or an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof.

4. The use of claim 3, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or an isotopic variant thereof, or polymorph thereof.

5. The use of any one of claims 1-4, wherein the neurological disorder is treatment-refractory obsessive-compulsive disorder (OCD).

6. The use of any one of claims 1-4, wherein the neurological disorder is mania in a mood disorder.

7. The use of any one of claims 1-5, wherein the treatment-refractory obsessive-compulsive disorder is characterized by one or more obsessive compulsive behaviors selected from cleaning, hoarding, a counting ritual, a checking ritual, a line-crossing, a prayer ritual, a hand washing ritual, following a strict routine, orderliness, requesting reassurance, or a combination thereof is reduced.

8. The use of any one of claims 1-4, and 6, wherein the mood disorder is bipolar disorder.

9. The use of claim 6, wherein the mania in the mood disorder is hypomania or severe mania.

10. The use of any one of claims 1-4, wherein the mood disorder is major depressive disorder.

11. The use of any one of claims 1-10, wherein the VMAT2 inhibitor is to be administered at a daily dose of about 5 mg to about 100 mg.

12. The use of any one of claims 1-11, wherein the VMAT2 inhibitor is to be administered orally.

13. The use of claim 12, wherein the VMAT2 inhibitor is to be administered as a tablet or capsule.

14. The use of claim 13, wherein the tablet or capsule contains about 5 mg to about 100 mg of the VMAT2 inhibitor.

15. The use of claim 14, wherein the tablet or capsule contains about 10 mg to about 80 mg of the VMAT2 inhibitor.

16. The use of claim 3, 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, or a pharmaceutically acceptable salt, or a polymorph thereof.

17. The use of claim 16, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or a polymorph thereof.

18. The use of claim 1 or 2, wherein the VMAT2 inhibitor is (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), or a pharmaceutically acceptable salt, or a polymorph thereof.

19. The use of claim 1 or 2, wherein the VMAT2 inhibitor is 3-isobutyl-9,10-d_6-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (d_6-TBZ), or a pharmaceutically acceptable salt, or a polymorph thereof.

20. The use of any one of claims 16-19, wherein the neurological disorder is mania in a mood disorder.

21. The use of any one of claims 16-20, wherein the mood disorder is bipolar disorder or major depressive disorder.

22. The use of any one of claims 16-19, wherein the neurological disorder is treatment-refractory obsessive-compulsive disorder (OCD).

23. The use of any one of claims 16-22, wherein the VMAT2 inhibitor is to be administered at a daily dose of about 5 mg to about 100 mg.

24. The use of any one of claims 16-23, wherein the VMAT2 inhibitor is to be administered orally.

25. The use of any one of claims 16-24, wherein the VMAT2 inhibitor is to be administered as a tablet or capsule.

26. The use of claim 25, wherein the tablet or capsule contains about 5 mg to about 100 mg of the VMAT2 inhibitor.

27. The use of claim 26, wherein the tablet or capsule contains about 10 mg to about 80 mg of the VMAT2 inhibitor.

28. Use of a VMAT2 inhibitor selected from:

(2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ); and

(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; or

an isotopic variant, a pharmaceutically acceptable salt, or a polymorph thereof,

in the manufacture of a medicament for the treatment of a neurological disorder, wherein the neurological disorder is depression in a mood disorder.

29. The use of claim 28, wherein the VMAT2 inhibitor is (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (R,R,R DHTBZ), a pharmaceutically acceptable salt, or a polymorph thereof.

30. The use of claim 28, 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, a pharmaceutically acceptable salt, or polymorph thereof.

31. The use of claim 30, wherein the VMAT2 inhibitor is (*S*)-(2*R*,3*R*,11b*R*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate), or a polymorph thereof.

32. The use of any one of claims 28-31, wherein the mood disorder is bipolar disorder.

33. The use of any one of claims 28-31, wherein the mood disorder is major depressive disorder.

34. The use of any one of claims 28-33, wherein the VMAT2 inhibitor is to be administered at a daily dose of about 5 mg to about 100 mg.

35. The use of any one of claims 28-34, wherein the VMAT2 inhibitor is to be administered orally.

36. The use of claim 35, wherein the VMAT2 inhibitor is to be administered as a tablet or capsule.

37. The use of claim 36, wherein the tablet or capsule contains about 5 mg to about 100 mg of the VMAT2 inhibitor.

38. The use of claim 37, wherein the tablet or capsule contains about 10 mg to about 80 mg of the VMAT2 inhibitor.