PSILOCYBIN AND AN ADJUNCTIVE SEROTONIN REUPTAKE INHIBITOR FOR USE IN THE TREATMENT OF TREATMENT-RESISTANT DEPRESSION

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims the benefit of U.S. Provisional Application 63/288,938 filed on December 13, 2021, the contents of which are hereby incorporated by reference in their entireties.

BACKGROUND

[0002] Depression is one of the most common mental illnesses, affecting more than 264 million people worldwide. It is characterized by depressed mood and markedly diminished interest or pleasure in activities. Other symptoms include significant weight loss or weight gain, decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate or indecisiveness, recurrent thoughts of death, suicidal ideation or suicidal attempts.

[0003] Current treatments for depression often consist of a combination of psychotherapy and one or more daily medications that regulate neurotransmitters such as dopamine, serotonin, and norepinephrine. These medications often take weeks to months to achieve their full effects and in the meantime, individuals continue to suffer from their symptoms and be at risk of self-harm, as well as harm to their personal and professional lives.

[0004] There remains a need in the art for an effective treatment for depression that provides a rapid onset of antidepressant effects within hours or a few days and is sustained long-term.

SUMMARY

[0005] The present disclosure provides methods of treating treatment-resistant depression in a subject in need thereof.

[0005a] In an aspect of the present disclosure, there is provided a use of psilocybin, or an active metabolite thereof, in the manufacture of a medicament for treating treatment-resistant depression in a subject in need thereof, wherein psilocybin, or an active metabolite thereof, is to be administered as an adjunctive to Selective Serotonin Reuptake Inhibitor (SSRI) therapy.

[0006] In some examples, the methods described herein comprise treating treatment-resistant depression in a subject in need thereof, comprising administering an effective amount of psilocybin or an active metabolite thereof to the subject as an adjunctive to Selective Serotonin Reuptake Inhibitor (SSRI) therapy.

[0007] In some examples, the SSRI is selected from the group consisting of escitalopram, sertraline, fluoxetine, vilazodone, vortioxetine, paroxetine or citalopram.

[0008] In some examples, the SSRI is administered prior to administration of psilocybin. In some examples, the SSRI is administered after administration of psilocybin. In some examples, the SSRI is administered on the same day as the psilocybin.

[0009] In some examples, about 25 mg of psilocybin or an active metabolite thereof is administered to the subject.

[0010] In some examples, at least one sign or symptom of depression is reduced by the administration of psilocybin. In some examples, the sign or symptom of depression is depressed mood, diminished interest in activities, weight loss or gain, decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to concentrate or indecisiveness, or suicidal ideation or behavior.

[0011] In some examples, the sign or symptom of depression is measured according to a diary assessment, an assessment by clinician or caregiver, a clinical rating scale, or by functional MRI. In some examples, the clinical rating scale is a Quick Inventory of Depressive Symptomatology (QIDS)-16 scale, a QIDS-16 daily scale, a Hamilton Depression Rating scale, a Beck Depression Inventory scale, a Montgomery-Asberg Depression Rating Scale (MADRS), a Clinical Global Impression Scale, a Zung Self-Rating Depression Scale, a Raskin Depression Rating Scale, and/or Young Mania Rating Scale.

[0012] In some examples, the clinical rating scale is MADRS. In someexamples, the administration of psilocybin provides an about 50% reduction in patient's MADRS total score compared to prior to treatment with psilocybin. In some examples, the administration of psilocybin provides a reduction in the patient's MADRS total score to ≤10.

[0013] In some examples, the clinical rating scale is Clinical Global Impression-Severity scale (CGI-S). In some examples, the administration of psilocybin provides a reduction in the patient's CGI-S score to ≤2. In some examples, the clinical rating scale is Clinical Global Impression-Improvement scale (CGI-I). In some examples, the administration of psilocybin provides a reduction in the patient's CGI-I score reported as "very much improved" or "much improved" compared to prior to treatment with psilocybin.

[0014] In some examples, the administration of psilocybin provides a reduction in the patient's anxiety compared to prior to treatment with psilocybin. In some examples, the administration of psilocybin provides a reduction in the patient's Generalised Anxiety Disorder-7 item scale (GAD-7) total score compared to prior to treatment with psilocybin.

[0015] In some examples, at least one sign or symptom of depression is alleviated within 24 hours of administration of the psilocybin. In some examples, at least one symptom of depression is alleviated within 1 week of administration of the psilocybin. In some examples, at least one symptom of depression is alleviated for a period of at least 1 month after administration of the psilocybin. In some examples, at least one symptom of depression is

alleviated for a period of at least 3 months after administration of the psilocybin. In some examples, at least one symptom of depression is alleviated for a period of at least 12 months after administration of the psilocybin.

[0016] In some examples, at least two doses of psilocybin are administered to the subject. In some examples, the psilocybin is administered once per day. In some examples, the psilocybin is administered at least once per week. In some examples, the psilocybin is administered at least twice per week. In some examples, the psilocybin is administered at least once per month. In some examples, the psilocybin is administered at least twice per month. In some examples, the psilocybin is administered at least once every three months. In some examples, the psilocybin is administered at least once every six months. In some examples, the psilocybin is administered at least once every 12 months. In some examples, each dose of psilocybin administered is about 25 mg.

[0017] In some examples, the psilocybin is administered by one of the following routes: oral, intravenous, intramuscular, parenteral, topical, inhalation, rectal, transmucosal, intranasal, buccal, vaginal, intrathecal, intraocular, transdermal, in utero, intralymphatic, or by direct tissue or organ injection. In some examples, the psilocybin is administered orally.

[0018] In some examples, the psilocybin comprises a crystalline polymorph of psilocybin. In some examples, the psilocybin comprises a crystalline polymorph of psilocybin. In some examples, the crystalline Polymorph A of psilocybin is characterized by XRPD peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θ. In some examples, the Polymorph A is further characterized by at least one peak selected from the group consisting of 20.4±0.1, 22.2±0.1, 24.3±0.1, and 25.7±0.1 °2θ.

[0019] In some examples, the crystalline psilocybin comprises Hydrate A. In some examples, the Hydrate A is characterized by X-ray powder diffraction (XRPD) peaks at 8.9±0.1, 13.8±0.1, 19.4±0.1, 23.1±0.1 and 23.5±0.1 °2θ. In some examples, the Hydrate A is further characterized by at least one peak selected from the group consisting of 6.5±0.1, 12.2±0.1, 12.6±0.1, 16.2±0.1, 20.4±0.1, 20.8±0.1, and 21.5±0.1°2θ.

[0020] In some examples, the psilocybin has no single impurity of greater than 1% as determined by HPLC analysis. In some examples, the psilocybin has a chemical purity of greater than 97% as determined by HPLC analysis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. 1 is a numbered structural formula of psilocybin.

[0022] FIG. 2A is a XRPD diffractogram of Polymorph A (GM764B).

CLAIMS

1. Use of psilocybin, or an active metabolite thereof, in the manufacture of a medicament for treating treatment-resistant depression in a subject in need thereof, wherein psilocybin, or an active metabolite thereof, is to be administered as an adjunctive to Selective Serotonin Reuptake Inhibitor (SSRI) therapy.

2. The use of claim 1, wherein the SSRI is selected from the group consisting of escitalopram, sertraline, fluoxetine, vilazodone, vortioxetine, paroxetine or citalopram.

3. The use of any one of claims 1-2, wherein the SSRI is to be administered prior to administration of psilocybin.

4. The use any one of claims 1-2, wherein the SSRI is to be administered after administration of psilocybin.

5. The use any one of claims 1-4, wherein the SSRI is to be administered on the same day as the psilocybin.

6. The use of any one of claims 1-5, wherein about 25 mg of psilocybin or an active metabolite thereof is to be administered to the subject.

7. The use of any one of claim 1-6, wherein at least one sign or symptom of depression is reduced by the administration of psilocybin.

8. The use of claim 7, wherein the sign or symptom of depression is depressed mood, diminished interest in activities, weight loss or gain, decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to concentrate or indecisiveness, or suicidal ideation or behavior.

9. The use of claim 7, wherein the sign or symptom of depression is measured according to a diary assessment, an assessment by clinician or caregiver, a clinical rating scale, or by functional MRI.

10. The use of claim 9, wherein the clinical rating scale is a Quick Inventory of Depressive Symptomatology (QIDS)-16 scale, a QIDS-16 daily scale, a Hamilton Depression Rating scale, a Beck Depression Inventory scale, a Montgomery-Asberg Depression Rating

Scale (MADRS), a Clinical Global Impression Scale, a Zung Self-Rating Depression Scale, a Raskin Depression Rating Scale, and/or Young Mania Rating Scale.

11. The use of claim 9, wherein the clinical rating scale is MADRS.

12. The use of claim 11, wherein the administration of psilocybin provides an about 50% reduction in patient's MADRS total score compared to prior to treatment with psilocybin.

13. The use of any of claims 11-12, wherein the administration of psilocybin provides a reduction in the patient's MADRS total score to ≤10.

14. The use of claim 9, wherein the clinical rating scale is Clinical Global Impression-Severity scale (CGI-S).

15. The use of claim 14, wherein the administration of psilocybin provides a reduction in the patient's CGI-S score to ≤2.

16. The use of claim 9, wherein the clinical rating scale is Clinical Global Impression-Improvement scale (CGI-I).

17. The use of claim 16, wherein the administration of psilocybin provides a reduction in the patient's CGI-I score reported as "very much improved" or "much improved" compared to prior to treatment with psilocybin.

18. The use of any one of claims 1-17, wherein the administration of psilocybin provides a reduction in the patient's anxiety compared to prior to treatment with psilocybin.

19. The use of claim 18, wherein the administration of psilocybin provides a reduction in the patient's Generalised Anxiety Disorder-7 item scale (GAD-7) total score compared to prior to treatment with psilocybin.

20. The use of any one of claims 1-19, wherein at least one sign or symptom of depression is alleviated within 24 hours of administration of the psilocybin.

21. The use of any one of claims 1-19, wherein at least one symptom of depression is alleviated within 1 week of administration of the psilocybin.

22. The use of any one of claims 1-21, wherein at least one symptom of depression is alleviated for a period of at least 1 month after administration of the psilocybin.

23. The use of any one of claims 1-21, wherein the at least one symptom of depression is alleviated for a period of at least 3 months after administration of the psilocybin.

24. The use of any one of claims 1-21, wherein the at least one symptom of depression is alleviated for a period of at least 12 months after administration of the psilocybin.

25. The use of any one of claims 1-24, wherein at least two doses of psilocybin are to be administered to the subject.

26. The use of any one of claims 1-24, wherein the psilocybin is to be administered once per day.

27. The use any one of claims 25-26, wherein the psilocybin is to be administered at least once per week.

28. The use any one of claims 25-26, wherein the psilocybin is to be administered at least twice per week.

29. The use any one of claims 25-26, wherein the psilocybin is to be administered at least once per month.

30. The use any one of claims 25-26, wherein the psilocybin is to be administered at least twice per month.

31. The use any one of claims 25-26, wherein the psilocybin is to be administered at least once every three months.

32. The use any one of claims 25-26, wherein the psilocybin is to be administered at least once every six months.

33. The use any one of claims 25-26, wherein the psilocybin is to be administered at least once every 12 months.

34. The use of any one of claims 25-33, wherein each dose of psilocybin to be administered is about 25 mg.

35. The use of any one of claims 1-34, wherein the psilocybin is to be administered by one of the following routes: oral, intravenous, intramuscular, parenteral, topical, inhalation, rectal, transmucosal, intranasal, buccal, vaginal, intrathecal, intraocular, transdermal, in utero, intralymphatic, or by direct tissue or organ injection.

36. The use of claim 35, wherein the psilocybin is to be administered orally.

37. The use of any one of any one of claims 1-36, wherein the psilocybin comprises a crystalline polymorph of psilocybin.

38. The use of claim 37, wherein the crystalline polymorph of psilocybin comprises Polymorph A.

39. The use of claim 38, wherein the crystalline Polymorph A of psilocybin is characterized by XRPD peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θ.

40. The use of claim 39, wherein the Polymorph A is further characterized by at least one peak selected from the group consisting of 20.4±0.1, 22.2±0.1, 24.3±0.1, and 25.7±0.1 °2θ.

41. The use of claim 37, wherein the crystalline psilocybin comprises Hydrate A.

42. The use of claim 41, wherein the Hydrate A is characterized by X-ray powder diffraction (XRPD) peaks at 8.9±0.1, 13.8±0.1, 19.4±0.1, 23.1±0.1 and 23.5±0.1 °2θ.

43. The use of claim 42, wherein the Hydrate A is further characterized by at least one peak selected from the group consisting of 6.5±0.1, 12.2±0.1, 12.6±0.1, 16.2±0.1, 20.4±0.1, 20.8±0.1, and 21.5±0.1°2θ.

44. The use of any one of claims 1-43, wherein the psilocybin has no single impurity of greater than 1% as determined by HPLC analysis.

45. The use of any one of claims 1-44, wherein the psilocybin has a chemical purity of greater than 97% as determined by HPLC analysis.