USE OF BENZODIAZEPINES TO INCREASE SENSITIVITY TO PSILOCYBIN FOLLOWING A CHRONIC SSRI REGIMEN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Application No. 63/094,624, filed October 21, 2020, which is hereby incorporated by reference in its entirety herein.

BACKGROUND

[0002] Psychedelics show significant promise in the treatment of several psychiatric indications. Current psychedelic administration guidelines recommend that patients on a chronic selective serotonin reuptake inhibitor (SSRI) regimen cease any SSRI therapy for at least 2 weeks prior to administration of psilocybin therapy, due to the observed impact of SSRIs on sensitivity to psilocybin. This leaves patients at risk, with no pharmacological support during this period of 'washout' and exposed to SSRI withdrawal symptoms. Therefore, there is a need to reduce this washout period such that patients who require psilocybin therapy would be unsupported for a shorter duration, reducing risk to the patient, improving the patient's experience, and increasing patient compliance.

SUMMARY

[0003] The present disclosure provides methods to reduce the SSRI washout period in patients prior to administration of psilocybin therapy.

[0003a] In an aspect of the present disclosure, there is provided a use of psilocybin in the manufacture of a medicament for administering to a subject in need thereof, wherein the psilocybin is to be administered to the subject, and prior to administration of psilocybin the subject was on a selective serotonin reuptake inhibitor (SSRI) therapy regimen comprising

a) ceasing SSRI therapy 1 to 35 days prior to administration of psilocybin; and

b) administering one or more benzodiazepines at least once daily to the subject starting at least 1 to 35 days prior to administration of psilocybin.

[0004] Provided herein is a method of administering psilocybin to a subject in need thereof, wherein prior to administration of psilocybin the subject was on a selective serotonin reuptake inhibitor (SSRI) therapy regimen comprising: a) ceasing SSRI therapy 1 to 35 days prior to administration of psilocybin; b) administering one or more benzodiazepines at least once daily to the subject starting at least 1 to 35 days prior to administration of psilocybin; and) administering psilocybin to the subject.

[0005] In some ~~embodiment~~examples, the SSRI therapy is ceased during a titration period, wherein during the titration period the dose of SSRI is reduced from a maintenance dose to cessation.

[0006] In some ~~embodiment~~examples, one or more benzodiazepines is administered during the SSRI titration period.

[0007] In some ~~embodiment~~examples, one or more benzodiazepines is administered after cessation of the SSRI.

[0008] In some ~~embodiment~~examples, one or more benzodiazepines is administered before the SSRI titration period.

[0009] In some ~~embodiment~~examples, SSRI therapy is ceased immediately, wherein immediate cessation of an SSRI does not comprise a titration period.

[0010] In some ~~embodiment~~examples, one or more benzodiazepines are administered after cessation of SSRI therapy.

[0011] In some ~~embodiment~~examples, one or more benzodiazepines are administered before cessation of SSRI therapy.

[0012] In some ~~embodiment~~examples, SSRI therapy is ceased 29 to 35 days prior to administration of psilocybin and one or more benzodiazepines are administered starting 1 to 28 days prior to administration of psilocybin.

[0013] In some ~~embodiment~~examples, SSRI therapy is ceased 22 to 35 days prior to administration of psilocybin and one or more benzodiazepines are administered starting 1 to 21 days prior to administration of psilocybin.

[0014] In some ~~embodiment~~examples, SSRI therapy is ceased 15 to 35 days prior to administration of psilocybin and one or more benzodiazepines are administered starting 1 to 14 days prior to administration of psilocybin.

[0015] In some ~~embodiment~~examples, SSRI therapy is ceased 8 to 35 days prior to administration of psilocybin and one or more benzodiazepines are administered starting 1 to 7 days prior to administration of psilocybin.

[0016] In some ~~embodiment~~examples, SSRI therapy is ceased 29 to 35 days prior to administration of psilocybin and one or more benzodiazepines are administered starting at least 35 days before administration of psilocybin.

[0017] In some ~~embodiment~~example**s**, SSRI therapy is ceased 22 to 35 days prior to administration of psilocybin and one or more benzodiazepines are administered starting at least 35 days before administration of psilocybin.

[0018] In some ~~embodiment~~example**s**, SSRI therapy is ceased 15 to 35 days prior to administration of psilocybin and one or more benzodiazepines are administered starting at least 35 days before administration of psilocybin.

[0019] In some ~~embodiment~~example**s**, SSRI therapy is ceased 8 to 35 days prior to administration of psilocybin and one or more benzodiazepines are administered starting at least 35 days before administration of psilocybin.

[0020] In some ~~embodiment~~example**s**, SSRI therapy is ceased in 1 to 35 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 28 days prior to administration of psilocybin.

[0021] In some ~~embodiment~~example**s**, SSRI therapy is ceased in 1 to 35 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 14 days prior to administration of psilocybin.

[0022] In some ~~embodiment~~example**s**, SSRI therapy is ceased in 1 to 35 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 7 days prior to administration of psilocybin.

[0023] In some ~~embodiment~~example**s**, SSRI therapy is ceased in 1 to 28 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 35 days prior to administration of psilocybin.

[0024] In some ~~embodiment~~example**s**, SSRI therapy is ceased in 1 to 28 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 28 days prior to administration of psilocybin.

[0025] In some ~~embodiment~~example**s**, SSRI therapy is ceased in 1 to 28 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 14 days prior to administration of psilocybin.

[0026] In some ~~embodiment~~example**s**, SSRI therapy is ceased in 1 to 28 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 7 days prior to administration of psilocybin.

[0027] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 35 days prior to administration of psilocybin.

[0028] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 28 days prior to administration of psilocybin.

[0029] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 21 days prior to administration of psilocybin.

[0030] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 14 days prior to administration of psilocybin.

[0031] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 7 days prior to administration of psilocybin.

[0032] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 35 days prior to administration of psilocybin.

[0033] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 28 days prior to administration of psilocybin.

[0034] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 21 days prior to administration of psilocybin.

[0035] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 14 days prior to administration of psilocybin.

[0036] In some ~~embodiment~~examples, SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and one or more benzodiazepines is administered 1 to 7 days prior to administration of psilocybin.

[0037] In some ~~embodiment~~examples, the maintenance SSRI daily dose is reduced by at least about 10 % every three to four days.

[0038] In some ~~embodiment~~examples, the maintenance SSRI daily dose is reduced by at least about 25 % every three to four days.

[0039] In some ~~embodiment~~examples, the maintenance SSRI daily dose is reduced by at least about 50 % every three to four days.

[0040] In some ~~embodiment~~examples, the maintenance SSRI daily dose is reduced by at least about 10 % every week.

[0041] In some ~~embodiment~~examples, the maintenance SSRI daily dose is reduced by at least about 25 % every week.

[0042] In some ~~embodiment~~examples, the maintenance SSRI daily dose is reduced by at least about 50 % every week.

[0043] In some ~~embodiment~~examples, the maintenance SSRI daily dose is reduced by at least about 10 % every other week.

[0044] In some ~~embodiment~~examples, the maintenance SSRI daily dose is reduced by at least about 25 % every other week.

[0045] In some ~~embodiment~~examples, the maintenance SSRI daily dose is reduced by at least about 50 % every other week.

[0046] In some ~~embodiment~~examples, reducing the maintenance SSRI daily dose starts between 1 and 16 weeks before administration of psilocybin.

[0047] In some ~~embodiment~~examples, reducing the maintenance SSRI daily dose starts between 1 and 12 weeks before administration of psilocybin.

[0048] In some ~~embodiment~~examples, reducing the maintenance SSRI daily dose starts between 1 and 8 weeks before administration of psilocybin.

[0049] In some ~~embodiment~~examples, reducing the maintenance SSRI daily dose starts between 1 and 4 weeks before administration of psilocybin.

[0050] In some ~~embodiment~~examples, reducing the maintenance SSRI daily dose starts between 1 and 2 weeks before administration of psilocybin.

[0051] In some ~~embodiment~~examples, the SSRI is ceased 14 days prior to administration of psilocybin.

[0052] In some ~~embodiment~~examples, the SSRI titration period comprises: a) administering to the subject 60-90% of the subject's maintenance dose of one or more SSRIs for 21 to 35 days prior to administration of psilocybin; b) administering to the subject 40-60% of the subject's maintenance dose of one or more SSRIs for 14 to 20 days prior to administration of psilocybin; c) administering to the subject 25-40% of the subject's maintenance dose of one or more SSRIs for 7 to 13 days prior to administration of psilocybin; and d) administering to the subject 5-25% of the subject's maintenance dose of one or more SSRIs for 1 to 6 days prior to administration of psilocybin.

[0053] In some ~~embodiment~~examples, the SSRI titration period comprises: a) administering to the subject 60-90% of the subject's maintenance dose of one or more SSRIs for 21 to 35 days prior to administration of psilocybin; b) administering to the subject 30-60% of the subject's maintenance dose of one or more SSRIs for 14 to 20 days prior to administration of psilocybin; c) administering to the subject 5-30% of the subject's maintenance dose of one or more SSRIs for 7 to 13 days prior to administration of psilocybin; and d) ceasing SSRI therapy 6 days prior to administration of psilocybin.

[0054] In some ~~embodiment~~examples, the SSRI is selected from the group consisting of citalopram, escitalopram, paroxetine, sertraline, fluvoxamine, fluoxetine, and combinations thereof.

[0055] In some ~~embodiment~~examples, the benzodiazepine is selected from the group consisting of alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, oxazepam, and combinations thereof.

[0056] In some ~~embodiment~~examples, at least one side effect of SSRI washout is reduced after treating according to the methods of the disclosure.

[0057] In some ~~embodiment~~examples, the at least one side effect of SSRI washout is selected from the group consisting of headache, asthenia, flu syndrome, fever, vasodilation, nausea, diarrhea, anorexia, dry mouth, dyspepsia, constipation, flatulence, vomiting, weight loss, insomnia, nervousness, anxiety, somnolence, dizziness, tremor, decreased libido, abnormal thinking, sweating, rash, pruritus, abnormal vision, dyspepsia, abdominal pain, fatigue, arthralgia, myalgia, somnolence, agitation, dysmenorrhea, decreased libido, yawning, upper respiratory tract infection, rhinitis, sinusitis, ejaculation disorder, ejaculatory delay, impotence, dysphoric mood,

irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), confusion, lethargy, emotional lability, and hypomania.

[0058] These and other examples and/or embodiments are addressed in more detail in the detailed description set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0059] FIG. 1 is a numbered structural formula of psilocybin.

[0060] FIG. 2A is a XRPD diffractogram of Polymorph A (GM764B).

[0061] FIG. 2B is a XRPD diffractogram of Polymorph A' (JCCA2160F).

[0062] FIG. 2C is a XRPD diffractogram of Polymorph B (JCCA2160-F-TM2).

[0063] FIG. 2D is a XRPD diffractogram of a Hydrate A (JCCA2157E).

[0064] FIG. 2E is a XRPD diffractogram of an ethanol solvate (JCCA2158D).

[0065] FIG. 2F is a XRPD diffractogram of product obtained during development of the process (CB646-E) (top) – compared to the diffractograms Polymorph A' (JCCA2160F) (middle) and Polymorph B (JCCA2160-TM2) (bottom).

[0066] FIG. 3A is a DSC and TGA thermograph of Polymorph A (GM764B).

[0067] FIG. 3B is a DSC and TGA thermograph of Polymorph A' (JCCA2160F).

[0068] FIG. 3C is a DSC thermograph of Polymorph B (GM748A).

[0069] FIG. 3D is a DSC and TGA thermograph of Hydrate A (JCCA2157E).

[0070] FIG. 3E is a DSC and TGA thermograph of ethanol solvate (JCCA2158D).

[0071] FIG. 4 is a form phase diagram showing the inter-relationship of form in water-based systems.

[0072] FIG. 5 is a 1H NMR spectrum of psilocybin.

[0073] FIG. 6 is a ^{13}C NMR spectrum of psilocybin.

[0074] FIG. 7 is a FT-IR Spectrum of psilocybin.

[0075] FIG. 8 is a Mass Spectrum of psilocybin.

[0076] FIG. 9A shows the effect of benzodiazepine pretreatment on ethovision activity to psilocybin at 5 minute intervals.

[0077] FIG. 9B shows the effect of benzodiazepine pretreatment on ethovision activity to psilocybin at 15 minute intervals.

CLAIMS

What is claimed is:

1. Use of psilocybin in the manufacture of a medicament for administering~~A method of administering psilocybin~~ to a subject in need thereof, wherein the psilocybin is to be administered to the subject, and prior to administration of psilocybin the subject was on a selective serotonin reuptake inhibitor (SSRI) therapy regimen comprising

a) ceasing SSRI therapy 1 to 35 days prior to administration of psilocybin; and

b) administering one or more benzodiazepines at least once daily to the subject starting at least 1 to 35 days prior to administration of psilocybin~~; and~~

~~c) administering psilocybin to the subject~~.

2. The ~~method~~use of claim 1, wherein SSRI therapy is ceased during a titration period, wherein during the titration period the dose of SSRI is reduced from a maintenance dose to cessation.

3. The ~~method~~use of claim 2, wherein one or more benzodiazepines is to be administered during the SSRI titration period.

4. The ~~method~~use of claim 2, wherein one or more benzodiazepines is to be administered after cessation of the SSRI.

5. The ~~method~~use of claim 2, wherein one or more benzodiazepines is to be administered before the SSRI titration period.

6. The ~~method~~use of claim 1, wherein SSRI therapy is ceased immediately, wherein immediate cessation of an SSRI does not comprise a titration period.

7. The ~~method~~use of claim 6, wherein one or more benzodiazepines are to be administered after cessation of SSRI therapy.

8. The ~~method~~use of claim 6, wherein one or more benzodiazepines are to be administered before cessation of SSRI therapy.

9. The ~~method~~use of any one of claims 1, 2, 4, 6, or 7, wherein SSRI therapy is ceased 29 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines are to be administered starting 1 to 28 days prior to administration of psilocybin.

10. The ~~method~~use of any one of claims 1, 2, 4, 6, or 7, wherein SSRI therapy is ceased 22 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines are to be administered starting 1 to 21 days prior to administration of psilocybin.

11. The ~~method~~use of any one of claims 1, 2, 4, 6, or 7, wherein SSRI therapy is ceased 15 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines are to be administered starting 1 to 14 days prior to administration of psilocybin.

12. The ~~method~~use of any one of claims 1, 2, 4, 6, or 7, wherein SSRI therapy is ceased 8 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines are to be administered starting 1 to 7 days prior to administration of psilocybin.

13. The ~~method~~use of any one of claims 1, 2, 5, 6, or 8, wherein SSRI therapy is ceased 29 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines are to be administered starting at least 35 days before administration of psilocybin.

14. The ~~method~~use of any one of claims 1, 2, 5, 6, or 8, wherein SSRI therapy is ceased 22 to 35 days prior to administration of psilocybin and wherein one or more

benzodiazepines are to be administered starting at least 35 days before administration of psilocybin.

15. The ~~method~~use of any one of claims 1, 2, 5, 6, or 8, wherein SSRI therapy is ceased 15 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines are to be administered starting at least 35 days before administration of psilocybin.

16. The ~~method~~use of any one of claims 1, 3, 6, 7, or 9, wherein SSRI therapy is ceased 8 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines are administered starting at least 35 days before administration of psilocybin.

17. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 28 days prior to administration of psilocybin.

18. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 14 days prior to administration of psilocybin.

19. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 35 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 7 days prior to administration of psilocybin.

20. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 28 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 35 days prior to administration of psilocybin.

21. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 28 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 28 days prior to administration of psilocybin.

22. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 28 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 14 days prior to administration of psilocybin.

23. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 28 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 7 days prior to administration of psilocybin.

24. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 35 days prior to administration of psilocybin.

25. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 28 days prior to administration of psilocybin.

26. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 21 days prior to administration of psilocybin.

27. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 14 days prior to administration of psilocybin.

28. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 14 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 7 days prior to administration of psilocybin.

29. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 35 days prior to administration of psilocybin.

30. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 28 days prior to administration of psilocybin.

31. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 21 days prior to administration of psilocybin.

32. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 14 days prior to administration of psilocybin.

33. The ~~method~~use of any one of the preceding claims, wherein SSRI therapy is ceased in 1 to 7 days prior to administration of psilocybin and wherein one or more benzodiazepines is to be administered 1 to 7 days prior to administration of psilocybin.

34. The ~~method~~use of claim 2, ~~comprising reducing~~wherein the maintenance SSRI daily dose is reduced by at least about 10 % every three to four days.

35. The ~~method~~use of claim 2, ~~comprising reducing~~wherein the maintenance SSRI daily dose is reduced by at least about 25 % every three to four days.

36. The ~~method~~use of claim 2, ~~comprising reducing~~wherein the maintenance SSRI daily dose is reduced by at least about 50 % every three to four days.

37. The ~~method~~use of claim 2, ~~comprising reducing~~wherein the maintenance SSRI daily dose is reduced by at least about 10 % every week.

38. The ~~method~~use of claim 2, ~~comprising reducing~~wherein the maintenance SSRI daily dose is reduced by at least about 25 % every week.

39. The ~~method~~use of claim 2, ~~comprising reducing~~wherein the maintenance SSRI daily dose is reduced by at least about 50 % every week.

40. The ~~method~~use of claim 2, ~~comprising reducing~~wherein the maintenance SSRI daily dose is reduced by at least about 10 % every other week.

41. The ~~method~~use of claim 2, ~~comprising reducing~~wherein the maintenance SSRI daily dose is reduced by at least about 25 % every other week.

42. The ~~method~~use of claim 2, ~~comprising reducing~~wherein the maintenance SSRI daily dose is reduced by at least about 50 % every other week.

43. The ~~method~~use of any one of claims 34-42, wherein ~~reducing~~ reduction of the maintenance SSRI daily dose starts between 1 and 16 weeks before administration of psilocybin.

44. The ~~method~~use of any one of claims 34-42, wherein ~~reducing~~ reduction of the maintenance SSRI daily dose starts between 1 and 12 weeks before administration of psilocybin.

45. The ~~method~~use of any one of claims 34-42, wherein ~~reducing~~ reduction of the maintenance SSRI daily dose starts between 1 and 8 weeks before administration of psilocybin.

46. The ~~method~~use of any one of claims 34-42, wherein ~~reducing~~ reduction of the maintenance SSRI daily dose starts between 1 and 4 weeks before administration of psilocybin.

47. The ~~method~~use of any one of claims 34-42, wherein ~~reducing~~ reduction of the maintenance SSRI daily dose starts between 1 and 2 weeks before administration of psilocybin.

48. The ~~method~~use of claim 1, wherein the SSRI is ceased 14 days prior to administration of psilocybin.

49. The ~~method~~use of claim 2, wherein during the SSRI titration period ~~comprises~~:

a) ~~administering to the subject~~ 60-90% of the subject's maintenance dose of one or more SSRIs is to be administered to the subject for 21 to 35 days prior to administration of psilocybin;

b) ~~administering to the subject~~ 40-60% of the subject's maintenance dose of one or more SSRIs is to be administered to the subject for 14 to 20 days prior to administration of psilocybin;

c) ~~administering to the subject~~ 25-40% of the subject's maintenance dose of one or more SSRIs is to be administered to the subject for 7 to 13 days prior to administration of psilocybin; and

d) ~~administering to the subject~~ 5-25% of the subject's maintenance dose of one or more SSRIs is to be administered to the subject for 1 to 6 days prior to administration of psilocybin.

50. The ~~method~~use of claim 2, wherein during the SSRI titration period ~~comprises~~:

a) ~~administering to the subject~~ 60-90% of the subject's maintenance dose of one or more SSRIs is to be administered to the subject for 21 to 35 days prior to administration of psilocybin;

b) ~~administering to the subject~~ 30-60% of the subject's maintenance dose of one or more SSRIs is to be administered to the subject for 14 to 20 days prior to administration of psilocybin;

c) ~~administering to the subject~~ 5-30% of the subject's maintenance dose of one or more SSRIs is to be administered to the subject for 7 to 13 days prior to administration of psilocybin; and

d) ~~ceasing~~ SSRI therapy is ceased 6 days prior to administration of psilocybin.

51. The ~~method~~use of any of the preceding claims, wherein the SSRI is selected from the group consisting of citalopram, escitalopram, paroxetine, sertraline, fluvoxamine, fluoxetine, and combinations thereof.

52. The ~~method~~use of any of the preceding claims, wherein the benzodiazepine is selected from the group consisting of alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, oxazepam, and combinations thereof.

53. The ~~method~~use of any of the preceding claims, wherein at least one side effect of SSRI washout is reduced.

54. The ~~method~~use of claim 52, wherein the at least one side effect of SSRI washout is selected from the group consisting of headache, asthenia, flu syndrome, fever, vasodilation, nausea, diarrhea, anorexia, dry mouth, dyspepsia, constipation, flatulence, vomiting, weight loss, insomnia, nervousness, anxiety, somnolence, dizziness, tremor, decreased libido, abnormal thinking, sweating, rash, pruritus, abnormal vision, dyspepsia, abdominal pain, fatigue, arthralgia, myalgia, somnolence, agitation, dysmenorrhea, decreased libido, yawning, upper respiratory tract infection, rhinitis, sinusitis, ejaculation disorder, ejaculatory delay, impotence, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), confusion, lethargy, emotional lability, and hypomania.

.