COMBINATION THERAPIES USING PSILOCYBIN

BACKGROUND

[0001] Psilocybin is known for its ability to produce alterations in consciousness and emotion, including various psychedelic effects. Psychedelic substances are presently under investigation for the treatment of several diseases and symptoms, including depression, PTSD, OCD, and addiction. From the clinical studies to date, the psychedelic experience is an integral part of the intended treatment. However, the effect of these substances on other biological processes is poorly understood.

[0002] Considerable efforts have been made to understand the mechanism of metabolic disorders so as to better design treatment modalities. Sarcopenia is a medical term describing the loss of skeletal muscle mass, in particular with aging or as a consequence of other diseases, for example liver diseases, that can impact overall health and quality of life. Sarcopenia may be triggered or worsened by metabolic disorder.

[0003] Accordingly, there is a need to develop new compositions, formulations, and methods for treating metabolic disorders and sarcopenia.

SUMMARY OF THE DISCLOSURE

[0004] The present disclosure provides methods of treating a metabolic disorder or sarcopenia in a patient in need thereof, comprising administering psilocybin, for example as an adjunctive therapy to another therapeutic.

[0005] In embodiments, the present disclosure provides a method of treating a metabolic disorder or sarcopenia in a patient in need thereof, the method comprising administering a therapeutically effective, non-psychedelic amount of psilocybin to the patient, wherein the psilocybin is administered as an adjunctive therapy to a GLP-1 receptor agonist.

[0006] In embodiments, the present disclosure provides a method of treating a metabolic disorder or sarcopenia in a patient in need thereof, the method comprising administering a therapeutically effective, non-psychedelic amount of psilocybin to the patient, wherein the psilocybin is administered as an adjunctive therapy to a biguanide.

[0007] In embodiments, the present disclosure provides a method of treating a metabolic disorder or sarcopenia in a patient in need thereof, the method comprising administering a therapeutically effective, non-psychedelic amount of psilocybin to the patient, wherein the psilocybin is administered as an adjunctive therapy to a PPARγ-agonist.

[0008] In embodiments, the present disclosure provides a method of treating a metabolic disorder or sarcopenia in a patient in need thereof, the method comprising administering a

therapeutically effective, non-psychedelic amount of psilocybin to the patient, wherein the psilocybin is administered as an adjunctive therapy to a sulfonylurea-based compound.

[0009] In embodiments, the present disclosure provides a method of treating a metabolic disorder or sarcopenia in a patient in need thereof, the method comprising administering a therapeutically effective, non-psychedelic amount of psilocybin to the patient, wherein the psilocybin is administered as an adjunctive therapy to a DPP-IV inhibitor.

[0010] In embodiments, the present disclosure provides a method of treating a metabolic disorder or sarcopenia in a patient in need thereof, the method comprising administering a therapeutically effective, non-psychedelic amount of psilocybin to the patient, wherein the psilocybin is administered as an adjunctive therapy to pramlintide.

[0011] In embodiments, the present disclosure provides a method of treating a metabolic disorder or sarcopenia in a patient in need thereof, the method comprising administering a therapeutically effective, non-psychedelic amount of psilocybin to the patient, wherein the psilocybin is administered as an adjunctive therapy to one or more amino acids, one or more vitamins, or one or more hormones.

[0012] In embodiments, the present disclosure provides a method of treating a metabolic disorder in a patient in need thereof, the method comprising co-administering to the patient:

(a) a non-psychedelic amount of psilocybin and

(b) a GLP-1 receptor agonist, metformin, a PPARγ-agonist, a sulfonylurea-based compound, a DPP-IV inhibitor, or pramlintide.

[0013] In embodiments, the metabolic disorder is prediabetes, type-II diabetes, obesity, metabolic dysfunction associated steatotic liver disease (MASLD and MetALD), metabolic dysfunction steatohepatitis (MASH), non-alcoholic fatty liver disease (NAFLD), liver steatosis, nonalcoholic steatohepatitis (NASH), or dyslipidemia. In embodiments, the disorder is sarcopenia.

[0014] Other embodiments will be readily apparent to the skilled person based on the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 is a graph showing the results of psilocin and semaglutide co-administration according to an embodiment of the present disclosure.

[0016] FIG. 2 shows fluorescence data of cells co-administered psilocin and semaglutide according to an embodiment of the present disclosure.

DETAILED DESCRIPTION

[0017] Combination treatments using psilocybin for the treatment of metabolic disorders and/or sarcopenia are disclosed herein. In particular,

Definitions

[0018] Throughout this disclosure, various patents, patent applications and publications (including non-patent publications) are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference for all purposes in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications cited and this disclosure.

[0019] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0020] The term "about" when immediately preceding a numerical value means a range (e.g., plus or minus 10% of that value). For example, "about 50" can mean 45 to 55, "about 25,000" can mean 22,500 to 27,500, etc., unless the context of the disclosure indicates otherwise, or is inconsistent with such an interpretation. For example, in a list of numerical values such as "about 49, about 50, about 55, …", "about 50" means a range extending to less than half the interval(s) between the preceding and subsequent values, e.g., more than 49.5 to less than 52.5. Similarly, the term "about" when preceding a series of numerical values or a range of values (e.g., "about 10, 20, 30" or "about 10-30") refers, respectively to all values in the series, or the endpoints of the range.

[0021] The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical formulation that is sufficient to result in a desired clinical benefit after administration to a patient or subject in need thereof.

[0022] In embodiments, an effective amount of psilocybin and/or GLP-1 receptor agonist, metformin, a PPARγ-agonist, a sulfonylurea-based compound, a DPP-IV inhibitor, or pramlintide is that amount that is required to reduce at least one symptom/biochemical marker of a metabolic disorder or sarcopenia as otherwise described herein in a patient. In embodiments, the therapeutically effective amount can vary depending upon the intended

application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The specific dose will vary depending on, for example, the dosing regimen to be followed, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0023] The term "treating" as used herein with regard to a patient, refers to improving at least one symptom/biochemical marker of the patient's disorder (for example, a metabolic disorder or sarcopenia). Treating can be improving, or at least partially ameliorating a disorder.

Psilocybin Administration

[0024] As described herein, a non-psychedelic amount of psilocybin may be administered as an adjunctive therapy to a GLP-1 receptor agonist, metformin, a PPARγ-agonist, a sulfonylurea-based compound, a DPP-IV inhibitor, or pramlintide. The psilocybin may be any suitable pharmaceutical salt thereof. Psilocybin derivatives are described, for example, in International Patent Application nos. PCT/US2020/021400 and PCT/US2022/028559, both of which are incorporated herein in their entirety. In embodiments, the psilocybin is pegylated psilocybin, or psilocin carbamate.

[0025] In embodiments, the non-psychedelic amount of psilocybin is about 0.1 mg to about 7 mg. In embodiments, the non-psychedelic amount of psilocybin is about 0.1 mg to about 6 mg, or about 0.1 mg to about 5 mg, or about 0.1 mg to about 4 mg, or about 0.1 mg to about 3 mg, or about 0.1 mg to about 2 mg, or about 0.1 mg to 1 mg, or about 0.2 mg to about 6 mg, or about 0.2 mg to about 5 mg, or about 0.2 mg to about 4 mg, or about 0.2 mg to about 3 mg, or about 0.2 mg to about 2 mg, or about 0.2 mg to 1 mg, or about0.3 mg to about 6 mg, or about 0.3 mg to about 5 mg, or about 0.3 mg to about 4 mg, or about 0.3 mg to about 3 mg, or about 0.3 mg to about 2 mg, or about 0.3 mg to 1 mg, or about 0.4 mg to about 6 mg, or about 0.4 mg to about 5 mg, or about 0.4 mg to about 4 mg, or about 0.4 mg to about 3 mg, or about 0.4 mg to about 2 mg, or about 0.4 mg to 1 mg. In embodiments, the non-psychedelic amount of psilocybin is about 0.5 mg, about 1 mg, about 2 mg, or about 3 mg, for example, about 0.5 mg.

[0026] In embodiments, the non-psychedelic amount of psilocybin is about 0.001 mg/kg to about 0.1 mg/kg, e.g., about 0.005 mg/kg to about 0.1 mg/kg.

[0027] In embodiments, the psilocybin is administered in an extended-release dosage form.

[0028] The psilocybin may be administered at various time points. In embodiments, the psilocybin is administered once a day, twice a day, or three times a day. In other embodiments,

the psilocybin is administered once every other week, once a week, twice a week, three times a week, four times a week, five times a week, or six times a week.

Combination Therapies

[0029] In embodiments, the present disclosure provides a method of treating a metabolic disorder or sarcopenia in a patient in need thereof, the method comprising administering a therapeutically effective, non-psychedelic amount of psilocybin to the patient, wherein the psilocybin is administered as an adjunctive therapy to a GLP-1 receptor agonist.

[0030] In embodiments, the GLP-1 agonist comprises dulaglutide, exenatide, semaglutide, liraglutide, or lixisenatide.

[0031] In embodiments, the GLP-1 agonist agonist is semaglutide. Semaglutide may be administered as known in the art. In embodiments, about 0.25 mg, about 0.5 mg, about 1 mg, about 2.4 mg, or about 3 mg of semaglutide is administered parenterally weekly to the patient. In embodiments, about 3 to about 21 mg of oral semaglutide is administered daily to the patient. In embodiments, about 3 mg, about 7 mg, or about 14 mg of oral semaglutide is administered daily to the patient.

[0032] In embodiments, the GLP-1 receptor agonist is dulaglutide. Dulaglutide may be administered as known in the art. In embodiments, about 0.75 mg, about 1.5 mg, or about 3 mg of dulaglutide is administered weekly to the patient.

[0033] In embodiments, the GLP-1 receptor agonist is exenatide. Exenatide may be administered as known in the art. In embodiments, about 5 mcg or about 10 mcg of exenatide is administered twice daily to the patient. In embodiments, the GLP1 receptor agonist is slow-release exenatide. Slow release exenatide may be administered as known in the art. In embodiments, about 1 or 2 mg of slow release exenatide is administered weekly to the patient.

[0034] In embodiments, the present disclosure provides a method of treating a metabolic disorder or sarcopenia in a patient in need thereof, the method comprising administering a therapeutically effective, non-psychedelic amount of psilocybin to the patient, wherein the psilocybin is administered as an adjunctive therapy to a biguanide.

[0035] In embodiments, the biguanide is metformin. Metformin may be administered as known in the art. In embodiments, about 850 mg to about 2550 mg of metformin hydrochloride is administered to the patient per day. In embodiments, about 500 mg of metformin hydrochloride is administered twice a day, or about 850 mg of metformin hydrochloride is administered once a day. In embodiments, about 500 mg, about 1000 mg, about 1500 mg, or

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