METHODS AND COMPOSITIONS FOR TREATING CONDITIONS ASSOCIATED WITH CENTRAL HYPOVENTILATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to and benefit of U.S. provisional application nos. 63/278,324, filed November 11, 2021, and 63/305,305, filed February 1, 2022, the entire contents of each of which are incorporated herein by reference.

TECHNICAL FIELD

[0002] The present invention provides pharmaceutical compositions comprising (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a carbonic anhydrase inhibitor, and methods of treating conditions associated with central hypoventilation.

BACKGROUND

[0003] Obesity hypoventilation syndrome (OHS) is a condition associated with obesity in which patients fail to breathe rapidly or deep enough, resulting in low oxygen levels and high blood CO_2 levels. Untreated OHS is associated with significant morbidity.

SUMMARY

[0004] One example of the present disclosure provides a method of treating a subject having a condition associated with central hypoventilation, the method comprising administering to a subject in need thereof an effective amount of (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a carbonic anhydrase inhibitor (CAI).

[0005] Examples of the present disclosure may include one or more of the following optional features. In some examples, the NRI is a norepinephrine selective reuptake inhibitor (NSRI). In some examples, the NSRI is selected from the group consisting of amedalin, atomoxetine, CP-39,332, daledalin, edivoxetine, esreboxetine, lortalamine, nisoxetine, reboxetine, talopram, talsupram, tandamine, and viloxazine, or a pharmaceutically acceptable salt thereof. In some examples, the NRI is a norepinephrine non-selective reuptake inhibitor (NNRI) selected from the group consisting of amitriptiline, amoxapine, bupropion, ciclazindol, desipramine, desvenlafaxine, dexmethilphenidate, diethylpropion, doxepin, duloxetine, imipramine, levomilnacipran, manifaxine, maprotiline, methylphenidate, milnacipran, nefazodone, nortriptyline, phendimetrazine, phenmetrazine, protryptyline, radafaxine, tapentadol, teniloxazine, and venlafaxine, or a pharmaceutically acceptable salt thereof. In some examples, the NRI is reboxetine or a pharmaceutically acceptable salt thereof. In some examples, the NRI is atomoxetine or a pharmaceutically acceptable salt thereof. In some examples, the CAI is selected from the group consisting

of acetazolamide, dichlorophenamide, dorzolamide, brinzolamide, methazolamide, zonisamide, ethoxzolamide, topiramate, sultiame, and any combination thereof, including pharmaceutically acceptable salts thereof. In some examples, the CAI is acetazolamide or a pharmaceutically acceptable salt thereof. In some examples, the NRI, such as atomoxetine or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 20 to about 200 mg. In some examples, the NRI, such as atomoxetine or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 to about 100 mg. In some examples, the CAI, such as acetazolamide, is administered at a dosage of from about 150 mg to about 750 mg. In some examples, the carbonic anhydrase inhibitor, such as acetazolamide, is administered at a dosage of about 500 mg. In some examples, the carbonic anhydrase inhibitor, such as acetazolamide, is administered at a dosage of about 250 mg. In some examples, the dose is a daily dose, i.e., administered once per day. In some examples, the dose is a twice-daily dose, i.e., administered in two administrations per day (e.g., once in the morning and once before bedtime). In some examples, the NRI and CAI are administered as separate compositions. In some examples, the NRI and CAI are administered in a single composition. In some examples, the separate compositions or single composition are an oral administration form. In some examples, the oral administration form is a syrup, pill, tablet, troche, capsule, or patch. In some examples, the condition associated with central hypoventilation is obesity hypoventilation syndrome (OHS) or obesity-related sleep hypoventilation (ORSH). In some examples, the condition associated with central hypoventilation is obesity hypoventilation syndrome (OHS). In some examples, the condition associated with central hypoventilation is obesity-related sleep hypoventilation (ORSH).

[0006] Another example of the present disclosure provides a pharmaceutical composition comprising (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a carbonic anhydrase inhibitor (CAI), and (iii) a pharmaceutically acceptable carrier.

[0007] Examples of the present disclosure may include one or more of the following optional features. In some examples, the NRI is a norepinephrine selective reuptake inhibitor (NSRI). In some examples, the NSRI is selected from the group consisting of amedalin, atomoxetine, CP-39,332, daledalin, edivoxetine, esreboxetine, lortalamine, nisoxetine, reboxetine, talopram, talsupram, tandamine, and viloxazine, or a pharmaceutically acceptable salt thereof. In some examples, the NRI is a norepinephrine non-selective reuptake inhibitor (NNRI) selected from the group consisting of amitriptiline,

amoxapine, bupropion, ciclazindol, desipramine, desvenlafaxine, dexmethilphenidate, diethylpropion, doxepin, duloxetine, imipramine, levomilnacipran, manifaxine, maprotiline, methylphenidate, milnacipran, nefazodone, nortriptyline, phendimetrazine, phenmetrazine, protryptyline, radafaxine, tapentadol, teniloxazine, and venlafaxine, or a pharmaceutically acceptable salt thereof. In some examples, the NRI is reboxetine or a pharmaceutically acceptable salt thereof. In some examples, the NRI is atomoxetine or a pharmaceutically acceptable salt thereof. In some examples, the CAI is selected from the group consisting of acetazolamide, dichlorophenamide, dorzolamide, brinzolamide, methazolamide, zonisamide, ethoxzolamide, topiramate, sultiame, and any combination thereof, including pharmaceutically acceptable salts thereof. In some examples, the CAI is acetazolamide or a pharmaceutically acceptable salt thereof. In some examples, the NRI, such as atomoxetine or a pharmaceutically acceptable salt thereof, is present in an amount of from about 20 to about 200 mg. In some examples, the NRI, such as atomoxetine or a pharmaceutically acceptable salt thereof, is present in an amount of from about 25 to about 100 mg. In some examples, the CAI, such as acetazolamide, is present in an amount of from about 150 mg to about 750 mg. In some examples, the carbonic anhydrase inhibitor, such as acetazolamide, is present in an amount of about 500 mg. In some examples, the carbonic anhydrase inhibitor, such as acetazolamide, is present in an amount of about 250 mg. In some examples, the NRI and CAI are formulated as separate compositions. In some examples, the NRI and CAI are formulated in a single composition. In some examples, the separate compositions or single composition are an oral administration form. In some examples, the oral administration form is a syrup, pill, tablet, troche, capsule, or patch. In some examples, the pharmaceutical composition is for use in treating a subject having a condition associated with central hypoventilation. In some examples, the condition associated with central hypoventilation is obesity hypoventilation syndrome (OHS) or obesity-related sleep hypoventilation (ORSH). In some examples, the condition associated with central hypoventilation is obesity hypoventilation syndrome (OHS). In some examples, the condition associated with central hypoventilation is obesity-related sleep hypoventilation (ORSH). In some examples, the pharmaceutical composition is administered daily. In some examples, the pharmaceutical composition is administered twice-daily.

[0007a] In a first aspect of the present disclosure, there is provided a use of a norepinephrine reuptake inhibitor (NRI) in the manufacture of a medicament for use in combinatorial therapy for treating a subject having a condition associated with central hypoventilation, wherein said medicament is to be administered in combination with a carbonic anhydrase inhibitor (CAI).

[0007b] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a carbonic anhydrase inhibitor (CAI), and (iii) a pharmaceutically acceptable carrier, in the manufacture of a medicament for treating a subject having a condition associated with central hypoventilation.

[0008] Also provided herein is a norepinephrine reuptake inhibitor (NRI) and a carbonic anhydrase inhibitor (CAI), for use in treating a subject having a condition associated with central hypoventilation.

[0009] Further provided herein is a therapeutic combination of (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a carbonic anhydrase inhibitor (CAI), for use in treating a subject having a condition associated with central hypoventilation.

[0009a] In yet another aspect of the present disclosure, there is provided a use of a therapeutic combination of (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a carbonic anhydrase inhibitor (CAI) in the manufacture of a medicament for treating a subject having a condition associated with central hypoventilation.

[0010] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this present disclosure belongs. Methods and materials are described herein for use in the present disclosure; other suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0011] Other features and advantages of the present disclosure will be apparent from the following detailed description and from the claims.

DETAILED DESCRIPTION

[0012] Obese subjects have an increased ventilator demand and an elevated work of breathing, in addition to slight respiratory muscle weakness and diminished respiratory compliance. Obese individuals generally have an increased central respiratory drive compared with normal weight patients to compensate for the increased ventilatory requirements. Despite this, in 20% of obese subjects (BMI > 30 kg/m^2) evaluated in sleep clinics, OSA is associated with diurnal hypercapnia ($PaCO_2$ > 45 mm Hg), which defines the obesity-hypoventilation syndrome (OHS) (1).

[0013] Compared to isolated OSA, OHS is characterized by increased morbidity and mortality due to cardiovascular and metabolic diseases associated with systemic inflammation, endothelial dysfunction and insulin resistance and the diagnosis is often made only after acute respiratory failure (2). However, OHS remains largely undiagnosed and untreated until patients require intensive care unit admission for acute decompensation (2, 3).

[0014] Lack in ventilatory responsiveness to gas alterations and insufficient ability to compensate to upper airway obstruction are pathophysiological implications of OHS. As the balance between obesity-related respiratory charge and ventilatory responsiveness to gas alterations may be conserved during daytime, it might be lost during sleep, determining initially an isolated nocturnal hypoventilation. Therefore, hypoventilation is most and primarily pronounced during sleep as a consequence of sleep-related physiological adaptations, which may or may not be also associated to sleep apnea. Indeed, it recently has been stated that isolated sleep hypoventilation (defined as a transcutaneous carbon dioxide

WHAT IS CLAIMED IS:

1. Use of a norepinephrine reuptake inhibitor (NRI) in the manufacture of a medicament for use in combinatorial therapy for treating a subject having a condition associated with central hypoventilation, wherein said medicament is to be administered in combination with a carbonic anhydrase inhibitor (CAI).

2. The use of claim 1, wherein the NRI is a norepinephrine selective reuptake inhibitor (NSRI).

3. The use of claim 2, wherein the NSRI is selected from the group consisting of amedalin, atomoxetine, CP-39,332, daledalin, edivoxetine, esreboxetine, lortalamine, nisoxetine, reboxetine, talopram, talsupram, tandamine, and viloxazine, or a pharmaceutically acceptable salt thereof.

4. The use of claim 1, wherein the NRI is a norepinephrine non-selective reuptake inhibitor (NNRI) selected from the group consisting of amitriptiline, amoxapine, bupropion, ciclazindol, desipramine, desvenlafaxine, dexmethilphenidate, diethylpropion, doxepin, duloxetine, imipramine, levomilnacipran, manifaxine, maprotiline, methylphenidate, milnacipran, nefazodone, nortriptyline, phendimetrazine, phenmetrazine, protryptyline, radafaxine, tapentadol, teniloxazine, and venlafaxine, or a pharmaceutically acceptable salt thereof.

5. The use of claim 1, wherein the NRI is reboxetine or a pharmaceutically acceptable salt thereof.

6. The use of claim 1, wherein the NRI is atomoxetine or a pharmaceutically acceptable salt thereof.

7. The use of any one of claims 1-6, wherein the CAI is selected from the group consisting of acetazolamide, dichlorophenamide, dorzolamide, brinzolamide, methazolamide, zonisamide, ethoxzolamide, topiramate, sultiame, and any combination thereof, or a pharmaceutically acceptable salt thereof.

8. The use of claim 7, wherein the CAI is acetazolamide or a pharmaceutically acceptable salt thereof.

9. The use of any one of claims 1-8, wherein the NRI, such as atomoxetine or a pharmaceutically acceptable salt thereof, is to be administered at a dosage of from about 20 to about 200 mg.

10. The use of claim 9, wherein the NRI, such as atomoxetine or a pharmaceutically acceptable salt thereof, is to be administered at a dosage of from about 25 to about 100 mg.

11. The use of any one of claims 1-10, wherein the CAI, such as acetazolamide, is to be administered at a dosage of from about 150 mg to about 750 mg.

12. The use of claim 11, wherein the carbonic anhydrase inhibitor, such as acetazolamide, is to be administered at a dosage of about 500 mg.

13. The use of claim 9 or 10, wherein the dosage of atomoxetine or a pharmaceutically acceptable salt thereof is to be administered in two separate administrations per day.

14. The use of claim 11 or 12, wherein the dosage of acetazolamide or a pharmaceutically acceptable salt thereof is to be administered in two separate administrations per day.

15. The use of claims 1-8, wherein the NRI is atomoxetine or a pharmaceutically acceptable salt thereof and is to be administered at a dosage of 25 to 100 mg, wherein the dosage of atomoxetine or a pharmaceutically acceptable salt thereof is to be administered in two separate administrations per day; and wherein the CAI is acetazolamide or a pharmaceutically acceptable salt thereof and is to be administered at a dosage of 250 to 750 mg, wherein the dosage of acetazolamide or a pharmaceutically acceptable salt thereof is to be administered in two separate administrations per day.

16. The use of any one of claims 1-15, wherein the NRI and CAI are to be administered as separate compositions.

17. The use of any one of claims 1-15, wherein the NRI and CAI are to be administered in a single composition.

18. The use of claim 16 or 17, wherein the separate compositions or single composition are an oral administration form.

19. The use of claim 18, wherein the oral administration form is a syrup, pill, tablet, troche, capsule, or patch.

20. The use of any one of claims 1-19, wherein the condition associated with central hypoventilation is obesity hypoventilation syndrome (OHS) or obesity-related sleep hypoventilation (ORSH).

21. The use of any one of claims 1-20, wherein the condition associated with central hypoventilation is obesity hypoventilation syndrome (OHS).

22. The use of any one of claims 1-20, wherein the condition associated with central hypoventilation is obesity-related sleep hypoventilation (ORSH).

23. Use of a pharmaceutical composition comprising (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a carbonic anhydrase inhibitor (CAI), and (iii) a pharmaceutically acceptable carrier, in the manufacture of a medicament for treating a subject having a condition associated with central hypoventilation.

24. The use of claim 23, wherein the NRI is a norepinephrine selective reuptake inhibitor (NSRI).

25. The use of claim 24, wherein the NSRI is selected from the group consisting of amedalin, atomoxetine, CP-39,332, daledalin, edivoxetine, esreboxetine, lortalamine, nisoxetine, reboxetine, talopram, talsupram, tandamine, and viloxazine, or a pharmaceutically acceptable salt thereof.

26. The use of claim 23, wherein the NRI is a norepinephrine non-selective reuptake inhibitor (NNRI) selected from the group consisting of amitriptiline, amoxapine, bupropion, ciclazindol, desipramine, desvenlafaxine, dexmethilphenidate, diethylpropion, doxepin, duloxetine, imipramine, levomilnacipran, manifaxine, maprotiline, methylphenidate, milnacipran, nefazodone, nortriptyline, phendimetrazine, phenmetrazine, protryptyline, radafaxine, tapentadol, teniloxazine, and venlafaxine, or a pharmaceutically acceptable salt thereof.

27. The use of claim 23, wherein the NRI is reboxetine or a pharmaceutically acceptable salt thereof.

28. The use of claim 23, wherein the NRI is atomoxetine or a pharmaceutically acceptable salt thereof.

29. The use of claim 23, wherein the CAI is selected from the group consisting of acetazolamide, dichlorophenamide, dorzolamide, brinzolamide, methazolamide, zonisamide, ethoxzolamide, topiramate, sultiame, or a pharmaceutically acceptable salt thereof.

30. The use of claim 29, wherein the CAI is acetazolamide or a pharmaceutically acceptable salt thereof.

31. The use of any one of claims 23-30, wherein the NRI, such as atomoxetine or pharmaceutically acceptable salt thereof, is present in an amount of from about 20 to about 200 mg.

32. The use of claim 31, wherein the NRI, such as atomoxetine or pharmaceutically acceptable salt thereof, is present in an amount of from about 25 to about 100 mg.

33. The use of any one of claims 23-32, wherein the CAI, such as acetazolamide, is present in an amount of from about 150 mg to about 750 mg.

34. The use of claim 33, wherein the CAI, such as acetazolamide, is present in an amount of about 500 mg.

35. The use of claim 33, wherein the CAI, such as acetazolamide or a pharmaceutically acceptable salt thereof, is to be administered at a dosage of about 250 mg.

36. The use of any one of claims 23-35, wherein the NRI and CAI are formulated in separate compositions.

37. The use of any one of claims 23-35, wherein the NRI and CAI are formulated in a single composition.

38. The use of claims 36 or 37, wherein the separate composition or single composition are an oral administration form.

39. The use of claim 38, wherein the oral administration form is a syrup, pill, tablet, troche, capsule, or patch.

40. The use of any one of claims 23-39, wherein the condition associated with central hypoventilation is obesity hypoventilation syndrome (OHS) or obesity-related sleep hypoventilation (ORSH).

41. The use of claim 40, wherein the condition associated with central hypoventilation is obesity hypoventilation syndrome (OHS).

42. The use of claim 40, wherein the condition associated with central hypoventilation is obesity-related sleep hypoventilation (ORSH).

43. The use of any one of claims 23-42, wherein the pharmaceutical composition is to be administered daily.

44. The use of claim 43, wherein the pharmaceutical composition is to be administered twice-daily.

45. Use of a therapeutic combination of (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a carbonic anhydrase inhibitor (CAI) in the manufacture of a medicament for treating a subject having a condition associated with central hypoventilation.