METHODS AND COMPOSITIONS FOR TREATING SLEEP APNEA

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to United States provisional application 63/165,342, filed March 24, 2021, the entire contents 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 mineralocorticoid antagonist, and optionally (iii) a muscarinic receptor antagonist (MRA), as well as methods of treating sleep apnea.

BACKGROUND

[0003] Obstructive Sleep Apnea (OSA) is a common disorder caused by collapse of the pharyngeal airway during sleep. OSA can have serious health consequences.

SUMMARY

[0004] In one aspect, the present disclosure provides a use of a norepinephrine reuptake inhibitor (NRI) and a mineralocorticoid antagonist in the manufacture of a medicament for combination therapy to treat a condition associated with pharyngeal airway collapse. In another aspect, the present disclosure provides a pharmaceutical composition comprising a norepinephrine reuptake inhibitor (NRI), a mineralocorticoid antagonist, and a pharmaceutically acceptable carrier. In yet another aspect, the present disclosure provides a kit comprising (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a mineralocorticoid antagonist, and optionally (iii) a muscarinic receptor antagonist (MRA) as a combined pharmaceutical formulation for use in treating a condition associated with pharyngeal airway collapse. In yet another aspect, the present disclosure provides a use of a norepinephrine reuptake inhibitor (NRI) in the manufacture of a medicament for use in combinatorial therapy for the treatment of a condition associated with pharyngeal airway collapse, wherein said medicament is to be administered in combination with a mineralocorticoid antagonist. In yet another aspect, the present disclosure provides a use of a mineralocorticoid antagonist in the manufacture of a medicament for use in combinatorial therapy for the treatment of a condition associated with pharyngeal airway collapse, wherein said medicament is to be administered in combination with a norepinephrine reuptake inhibitor (NRI). In yet another aspect, the present disclosure provides a use of a norepinephrine reuptake inhibitor (NRI) in the manufacture of a first medicament and use of a mineralocorticoid antagonist in the manufacture of a second medicament, wherein the first and second medicaments are to be

used in combination therapy to treat a condition associated with pharyngeal airway collapse. One example of the present disclosure provides a method of treating a subject having a condition associated with pharyngeal airway collapse, the method comprising administering to a subject in need thereof an effective amount of (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a mineralocorticoid antagonist.

[0005] Examples of this aspect of the 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 selected from the group consisting of atomoxetine or a pharmaceutically acceptable salt thereof and reboxetine or a pharmaceutically acceptable salt thereof. In some examples, the NRI is atomoxetine or a pharmaceutically acceptable salt thereof. In some examples, the mineralocorticoid antagonist is selected from the group consisting of spironolactone, eplerenone, canrenone,

finerenone, mexrenone, canrenoic acid, drospirenone, prorenone, apararenone, and esaxerenone, or a pharmaceutically acceptable salt thereof. In some examples, the mineralocorticoid antagonist is spironolactone or a pharmaceutically acceptable salt thereof. In some examples, the mineralocorticoid antagonist is spironolactone. In some examples, the method further comprises administering to the subject (iii) a muscarinic receptor antagonist (MRA). In some examples, the MRA is selected from the group consisting of atropine, propantheline, bethanechol, solifenacin, darifenacin, tolterodine, fesoterodine, trospium, and oxybutynin, or a pharmaceutically acceptable salt thereof. In some examples, the MRA is selected from the group consisting of anisotropine, benztropine, biperiden, clidinium, cycrimine, dicyclomine, diphemanil, diphenidol, ethopropazine, glycopyrrolate, hexocyclium, isopropamide, mepenzolate, methixene, methscopolamine, oxyphencyclimine, oxyphenonium, procyclidine, scopolamine, tridihexethyl, and trihexyphenidyl, or a pharmaceutically acceptable salt thereof. In some examples, the MRA is oxybutynin or a pharmaceutically acceptable salt thereof. In some examples, the MRA is (R)-oxybutynin or a pharmaceutically acceptable salt thereof. In some examples, the atomoxetine or pharmaceutically acceptable salt thereof is administered at a dose of from about 20 to about 200 mg. In some examples, the atomoxetine or pharmaceutically acceptable salt thereof is administered at a dose of from about 25 to about 100 mg. In some examples, the spironolactone or pharmaceutically acceptable salt thereof is administered at a dose of from about 10 to about 100 mg. In some examples, the spironolactone or pharmaceutically acceptable salt thereof is administered at a dose of from about 20 to about 80 mg. In some examples, the oxybutynin or pharmaceutically acceptable salt thereof is administered at a dose of from about 1 to about 15 mg. In some examples, the oxybutynin or pharmaceutically acceptable salt thereof is administered at a dose of from about 2 mg to about 10 mg. In some examples, the (R)-oxybutynin or pharmaceutically acceptable salt thereof is administered at a dose of from about 0.5 to about 10 mg. In some examples, the (R)-oxybutynin or pharmaceutically acceptable salt thereof is administered at a dose of from about 1 mg to about 5 mg. In some examples, the NRI and mineralocorticoid antagonist are administered in a single composition. In some examples, the NRI, MRA, and mineralocorticoid antagonist are administered in a single composition. In some examples, the single composition is 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 pharyngeal airway collapse is sleep apnea. In some examples, the condition associated

with pharyngeal airway collapse is obstructive sleep apnea (OSA). In some examples, the condition associated with pharyngeal airway collapse is snoring. In some examples, the condition associated with pharyngeal airway collapse is simple snoring. In some examples, the subject is in a non-fully conscious state. In some examples, the non-fully conscious state is sleep. In some examples, the subject has hypertension.

[0006] Another example of the disclosure provides a pharmaceutical composition comprising (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a mineralocorticoid antagonist, in a pharmaceutically acceptable carrier.

[0007] Examples of this aspect of the 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 selected from the group consisting of atomoxetine or a pharmaceutically acceptable salt thereof and reboxetine or a pharmaceutically acceptable salt thereof. In some examples, the NRI is atomoxetine or a pharmaceutically acceptable salt thereof. In some examples, the mineralocorticoid antagonist is selected from the group consisting of spironolactone, eplerenone, canrenone, finerenone, mexrenone, canrenoic acid, drospirenone, prorenone, apararenone, and esaxerenone, or a pharmaceutically acceptable salt thereof. In some examples, the mineralocorticoid antagonist is spironolactone or a pharmaceutically acceptable salt thereof. In some examples, the mineralocorticoid antagonist is spironolactone. In some examples, the composition further comprises (iii) a muscarinic receptor antagonist (MRA). In some examples, the MRA is selected from the group consisting of atropine, propantheline, bethanechol, solifenacin, darifenacin, tolterodine, fesoterodine, trospium, and oxybutynin, or a pharmaceutically acceptable salt thereof. In some examples, the MRA is selected from the group consisting of anisotropine, benztropine, biperiden, clidinium, cycrimine, dicyclomine, diphemanil, diphenidol, ethopropazine, glycopyrrolate,

hexocyclium, isopropamide, mepenzolate, methixene, methscopolamine, oxyphencyclimine, oxyphenonium, procyclidine, scopolamine, tridihexethyl, and trihexyphenidyl, or a pharmaceutically acceptable salt thereof. In some examples, the MRA is oxybutynin or a pharmaceutically acceptable salt thereof. In some examples, the MRA is (R)-oxybutynin or a pharmaceutically acceptable salt thereof. In some examples, the atomoxetine or pharmaceutically acceptable salt thereof is present in an amount of from about 20 to about 200 mg. In some examples, the atomoxetine or pharmaceutically acceptable salt thereof is present in an amount of from about 25 to about 100 mg. In some examples, the spironolactone or pharmaceutically acceptable salt thereof is present in an amount of from about 10 to about 100 mg. In some examples, the spironolactone or pharmaceutically acceptable salt thereof is present in an amount of from about 20 to about 80 mg. In some examples, the oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from about 1 to about 15 mg. In some examples, the oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from about 2 mg to about 10 mg. In some examples, the (R)-oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from about 0.5 to about 10 mg. In some examples, the (R)-oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from about 1 mg to about 5 mg. In some examples, the NRI and mineralocorticoid antagonist are formulated in a single composition. In some examples, the NRI, MRA, and mineralocorticoid antagonist are formulated in a single composition. In some examples, the single composition is an oral administration form. In some examples, the oral administration form is a syrup, pill, tablet, troche, capsule, or patch. In some examples, the composition is for use in treating a subject having a condition associated with pharyngeal airway collapse. In some examples, the condition associated with pharyngeal airway collapse is sleep apnea. In some examples, the condition associated with pharyngeal airway collapse is obstructive sleep apnea (OSA). In some examples, the condition associated with pharyngeal airway collapse is snoring. In some examples, the condition associated with pharyngeal airway collapse is simple snoring. In some examples, the subject is in a non-fully conscious state. In some examples, the non-fully conscious state is sleep. In some examples, the subject has hypertension.

[0008] Another example of the disclosure provides a kit comprising (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a mineralocorticoid antagonist, and optionally (iii) a muscarinic receptor antagonist. In some examples, the kit is for use in treating a subject having a condition associated with pharyngeal airway collapse.

[0009] Another example of the disclosure provides a norepinephrine reuptake inhibitor (NRI) and a mineralocorticoid antagonist, and optionally a muscarinic receptor antagonist, for use in treating a subject having a condition associated with pharyngeal airway collapse.

[0010] Another example of the disclosure provides a therapeutic combination of (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a mineralocorticoid antagonist, and optionally (iii) a muscarinic receptor antagonist, for use in treating a subject having a condition associated with pharyngeal airway collapse.

[0011] 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 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.

[0012] Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The following figures are provided by way of example and are not intended to limit the scope of the claimed invention.

[0014] FIG. 1 is a graphic illustration of an obstructive apnea. The top channel shows the electroencephalogram (EEG) pattern of sleep. The next channel represents airflow. The next three channels show ventilator effort by movements of the rib cage and abdomen and changes in esophageal pressure, all of which reflect a respiratory effort against an occluded upper airway. The last channel indicates oxyhemoglobin saturation.

[0015] FIG. 2 is a diagram showing the study design of Example 1.

DETAILED DESCRIPTION

[0016] In humans, the pharyngeal airway region has no bone or cartilage support, and it is held open by muscles. When these muscles relax during sleep, the pharynx can collapse resulting in cessation of airflow. As shown in Fig. 1, ventilatory effort continues and increases in an attempt to overcome the obstruction, shown by an increase in esophageal pressure change. Rib cage and abdominal movements are in the opposite direction as a result of the diaphragm contracting against an occluded airway, forcing the abdominal wall to distend out and the chest wall to cave inward.

WHAT IS CLAIMED IS:

1. Use of a norepinephrine reuptake inhibitor (NRI) and a mineralocorticoid antagonist in the manufacture of a medicament for combination therapy to treat a condition associated with pharyngeal airway collapse.

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 selected from the group consisting of atomoxetine or a pharmaceutically acceptable salt thereof and reboxetine or a pharmaceutically acceptable salt thereof.

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

7. The use of any one of claims 1-6, wherein the mineralocorticoid antagonist is selected from the group consisting of spironolactone, eplerenone, canrenone, finerenone, mexrenone, canrenoic acid, drospirenone, prorenone, apararenone, and esaxerenone, or a pharmaceutically acceptable salt thereof.

8. The use of claim 7, wherein the mineralocorticoid antagonist is spironolactone or a pharmaceutically acceptable salt thereof.

9. The use of claim 8, wherein the mineralocorticoid antagonist is spironolactone.

10. The use of any one of claims 1-9, further comprising a muscarinic receptor antagonist (MRA) in the manufacture of the medicament for the treatment of the condition associated with pharyngeal airway collapse.

11. The use of claim 10, wherein the MRA is selected from the group consisting of atropine, propantheline, bethanechol, solifenacin, darifenacin, tolterodine, fesoterodine, trospium, and oxybutynin, or a pharmaceutically acceptable salt thereof.

12. The use of any claim 10, wherein the MRA is selected from the group consisting of anisotropine, benztropine, biperiden, clidinium, cycrimine, dicyclomine, diphemanil, diphenidol, ethopropazine, glycopyrrolate, hexocyclium, isopropamide, mepenzolate, methixene, methscopolamine, oxyphencyclimine, oxyphenonium, procyclidine, scopolamine, tridihexethyl, and trihexyphenidyl, or a pharmaceutically acceptable salt thereof.

13. The use of claim 11, wherein the MRA is oxybutynin or a pharmaceutically acceptable salt thereof.

14. The use of claim 13, wherein the MRA is (R)-oxybutynin or a pharmaceutically acceptable salt thereof.

15. The use of any one of claims 1-14, further comprising an additional active agent, which is a diuretic, in the manufacture of the medicament for the treatment of the condition associated with pharyngeal airway collapse.

16. The use of claim 15, wherein the diuretic is selected from the group consisting of chlorothiazide, hydrochlorothiazide, bendroflumethiazide, chlorthalidone, methychlothiazide, polythiazide, triamterene, furosemide, ethacrynic acid, metolazone, bumetanide, indapamide, amiloride, and torsemide or a pharmaceutically acceptable salt thereof.

17. The use of any one of claims 1-16, wherein the atomoxetine or pharmaceutically acceptable salt thereof is in an amount of from 20 to 200 mg.

18. The use of claim 17 wherein the atomoxetine or pharmaceutically acceptable salt thereof is present in an amount of from 25 to 100 mg.

19. The use of any one of claims 1-18, wherein the spironolactone or pharmaceutically acceptable salt thereof is present in an amount of from 10 to 100 mg.

20. The use of claim 19, wherein the spironolactone or pharmaceutically acceptable salt thereof is present in an amount of from 20 to 80 mg.

21. The use of any one of claims 10-20, wherein the oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from 1 to 15 mg.

22. The use of claim 21, wherein the oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from 2 mg to 10 mg.

23. The use of any one of claims 10-20, wherein the (R)-oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from 0.5 to 10 mg.

24. The use of claim 23, wherein the (R)-oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from 1 mg to 5 mg.

25. The use of any one of claims 1-24, wherein the medicament is an oral administration form.

26. The use of claim 25, wherein the oral administration form is a syrup, pill, tablet, troche, or capsule.

27. The use of any one of claims 1-26, wherein the condition associated with pharyngeal airway collapse is sleep apnea.

28. The use of claim 27, wherein the condition associated with pharyngeal airway collapse is obstructive sleep apnea (OSA).

29. The use of any one of claims 1-26, wherein the condition associated with pharyngeal airway collapse is snoring.

30. The use of claim 29 wherein the condition associated with pharyngeal airway collapse is simple snoring.

31. The use of any one of claims 1-30, wherein the treatment is for a subject in a non-fully conscious state, such as sleep.

32. The use of any one of claims 1-31, wherein the treatment is for a subject suffering from hypertension.

33. A pharmaceutical composition comprising a norepinephrine reuptake inhibitor (NRI), a mineralocorticoid antagonist, and a pharmaceutically acceptable carrier.

34. The composition of claim 33, wherein the NRI is a norepinephrine selective reuptake inhibitor (NSRI).

35. The composition of claim 34, 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.

36. The composition of claim 33, 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.

37. The composition of claim 33, wherein the NRI is selected from the group consisting of atomoxetine or a pharmaceutically acceptable salt thereof and reboxetine or a pharmaceutically acceptable salt thereof.

38. The composition of claim 37, wherein the NRI is atomoxetine or a pharmaceutically acceptable salt thereof.

39. The composition of any one of claims 33-38, wherein the mineralocorticoid antagonist is selected from the group consisting of spironolactone, eplerenone, canrenone, finerenone, mexrenone, canrenoic acid, drospirenone, prorenone, apararenone, and esaxerenone, or a pharmaceutically acceptable salt thereof.

40. The composition of claim 39, wherein the mineralocorticoid antagonist is spironolactone or a pharmaceutically acceptable salt thereof.

41. The composition of claim 40, wherein the mineralocorticoid antagonist is spironolactone.

42. The composition of any one of claims 33-41, further comprising a muscarinic receptor antagonist (MRA).

43. The composition of claim 42, wherein the MRA is selected from the group consisting of atropine, propantheline, bethanechol, solifenacin, darifenacin, tolterodine, fesoterodine, trospium, and oxybutynin, or a pharmaceutically acceptable salt thereof.

44. The composition of claim 42, wherein the MRA is selected from the group consisting of anisotropine, benztropine, biperiden, clidinium, cycrimine, dicyclomine, diphemanil, diphenidol, ethopropazine, glycopyrrolate, hexocyclium, isopropamide, mepenzolate, methixene, methscopolamine, oxyphencyclimine, oxyphenonium, procyclidine, scopolamine, tridihexethyl, and trihexyphenidyl, or a pharmaceutically acceptable salt thereof.

45. The composition of claim 43, wherein the MRA is oxybutynin or a pharmaceutically acceptable salt thereof.

46. The composition of claim 45, wherein the MRA is (R)-oxybutynin or a pharmaceutically acceptable salt thereof.

47. The composition of any one of claims 33-46, further comprising an additional active agent, which is a diuretic.

48. The composition of claim 47, wherein the diuretic is selected from the group consisting of chlorothiazide, hydrochlorothiazide, bendroflumethiazide, chlorthalidone, methychlothiazide, polythiazide, triamterene, furosemide, ethacrynic acid, metolazone, bumetanide, indapamide, amiloride, and torsemide or a pharmaceutically acceptable salt thereof.

49. The composition of any one of claims 33-48, wherein the atomoxetine or pharmaceutically acceptable salt thereof is present in an amount of from 20 to 200 mg.

50. The composition of claim 49, wherein the atomoxetine or pharmaceutically acceptable salt thereof is present in an amount of from 25 to 100 mg.

51. The composition of any one of claims 33-50, wherein the spironolactone or pharmaceutically acceptable salt thereof is present in an amount of from 10 to 100 mg.

52. The composition of claim 51, wherein the spironolactone or pharmaceutically acceptable salt thereof is present in an amount of from 20 to 80 mg.

53. The composition of any one of claims 42-52, wherein the oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from 1 to 15 mg.

54. The composition of claim 53, wherein the oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from 2 mg to 10 mg.

55. The composition of any one of claims 42-52, wherein the (R)-oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from 0.5 to 10 mg.

56. The composition of claim 55, wherein the (R)-oxybutynin or pharmaceutically acceptable salt thereof is present in an amount of from 1 mg to 5 mg.

57. The composition of any one of claims 33-56, wherein the composition is an oral administration form.

58. The composition of claim 57, wherein the oral administration form is a syrup, pill, tablet, troche, or capsule.

59. A kit comprising (i) a norepinephrine reuptake inhibitor (NRI) and (ii) a mineralocorticoid antagonist, and optionally (iii) a muscarinic receptor antagonist (MRA) as a combined pharmaceutical formulation for use in treating a condition associated with pharyngeal airway collapse.

60. Use of a norepinephrine reuptake inhibitor (NRI) in the manufacture of a medicament for use in combinatorial therapy for the treatment of a condition associated with pharyngeal airway collapse, wherein said medicament is to be administered in combination with a mineralocorticoid antagonist.

61. Use of a mineralocorticoid antagonist in the manufacture of a medicament for use in combinatorial therapy for the treatment of a condition associated with pharyngeal airway collapse, wherein said medicament is to be administered in combination with a norepinephrine reuptake inhibitor (NRI).

62. Use of a norepinephrine reuptake inhibitor (NRI) in the manufacture of a first medicament and use of a mineralocorticoid antagonist in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a condition associated with pharyngeal airway collapse.

63. The use of any of claims 60-62, wherein the mineralocorticoid antagonist is spironolactone or a pharmaceutically acceptable salt thereof.

64. The use of any of claims 60-63, wherein the NRI is atomoxetine or a pharmaceutically acceptable salt thereof.

65. The use of any of claims 60-64, wherein the condition associated with pharyngeal airway collapse is obstructive sleep apnea.