NOREPINEPHRINE REUPTAKE INHIBITORS FOR TREATING SLEEP APNEA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119 (a) and (e) of and priority to United States Provisional Application No. 63/211,673, filed June 17, 2021, and United States Provisional Application No. 63/319,035, filed March 11, 2022, the entire contents of each of which are incorporated herein by reference.

TECHNICAL FIELD

[0002] The present invention provides methods of treating sleep apnea and snoring comprising administering a norepinephrine reuptake inhibitor, optionally in the absence of an antimuscarinic therapy, and optionally wherein the method of treatment is a monotherapy.

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

[0003a] In an aspect of the present disclosure, there is provided a use of a norepinephrine reuptake inhibitor (NRI) in the manufacture of a medicament for treating a subject having a condition associated with pharyngeal airway collapse, wherein the NRI is to be administered in the absence of an antimuscarinic therapy.

[0003b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising (i) edivoxetine or a pharmaceutically acceptable salt thereof, (ii) trazodone or a pharmaceutically acceptable salt thereof, and (ii) a pharmaceutically acceptable excipient or carrier.

[0003c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising (i) viloxazine or a pharmaceutically acceptable salt thereof, (ii) trazodone or a pharmaceutically acceptable salt thereof, and (ii) a pharmaceutically acceptable excipient or carrier.

[0003d] In another aspect of the present disclosure, there is provided a use of edivoxetine or a pharmaceutically acceptable salt thereof, and trazodone or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a condition associated with pharyngeal airway collapse.

[0003e] In a further aspect of the present disclosure, there is provided a use of viloxazine or a pharmaceutically acceptable salt thereof, and trazodone or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a condition associated with pharyngeal airway collapse.

[0004] 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 a norepinephrine reuptake inhibitor (NRI).

[0005] Examples of the disclosure may include one or more of the following optional features. In some examples, the method is performed in the absence of an antimuscarinic therapy. In some examples, the method excludes an antimuscarinic therapy. In some examples, the subject does not concurrently receive an antimuscarinic therapy, i.e., is not concurrently administered an antimuscarinic agent. In some examples, the NRI is reboxetine or a pharmaceutically acceptable salt thereof. In some examples, the NRI is edivoxetine or a pharmaceutically acceptable salt thereof. In some examples, the NRI is viloxazine or a pharmaceutically acceptable salt thereof. In some examples, the method is a monotherapy with reboxetine or a pharmaceutically acceptable salt thereof as the sole active pharmaceutical ingredient. In some examples, the reboxetine or pharmaceutically acceptable salt thereof is administered at a dosage of from about 1 mg to about 8 mg. In some examples, the reboxetine or pharmaceutically acceptable salt thereof is administered at a dosage of from about 2 mg to about 6 mg. In some examples, the reboxetine is administered daily. In some examples, the reboxetine or pharmaceutically acceptable salt thereof is (S,S)-reboxetine or a

pharmaceutically acceptable salt thereof. In some examples, the NRI is atomoxetine or a pharmaceutically acceptable salt thereof. In some examples, the method is a monotherapy with edivoxetine or a pharmaceutically acceptable salt thereof as the sole active pharmaceutical ingredient. In some examples, the edivoxetine or pharmaceutically acceptable salt thereof is administered at a dosage of from about 5 mg to about 50 mg. In some examples, the edivoxetine or pharmaceutically acceptable salt thereof is administered at a dosage of from about 6 mg to about 36 mg. In some examples, the edivoxetine is administered daily. In some examples, the edivoxetine is administered in combination with oxybutynin, e.g., at a dose of from about 1 to about 20 mg of oxybutynin. The oxybutynin may be racemic oxybutynin or substantially enantiomerically pure R-oxybutynin. In some examples, the edivoxetine is administered in combination with trazodone or a pharmaceutically acceptable salt thereof, e.g., at a dose of from about 12.5 to about 200 mg. In some examples, the method is a monotherapy with viloxazine or a pharmaceutically acceptable salt thereof as the sole active pharmaceutical ingredient. In some examples, the viloxazine or pharmaceutically acceptable salt thereof is administered at a dosage of from about 50 mg to about 800 mg. In some examples, the viloxazine is administered daily. In some examples, the viloxazine is administered in combination with oxybutynin, e.g., at a dose of from about 1 to about 20 mg of oxybutynin. The oxybutynin may be racemic oxybutynin or substantially enantiomerically pure R-oxybutynin. In some examples, the viloxazine is administered in combination with trazodone or a pharmaceutically acceptable salt thereof, e.g., at a dose of from about 12.5 to about 200 mg. In some examples, the condition associated with pharyngeal airway collapse is sleep apnea, e.g., obstructive sleep apnea (OSA). In some examples, the condition associated with pharyngeal airway collapse is snoring, e.g., 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 NRI or pharmaceutically acceptable salt thereof is administered in an oral administration form. In some examples, the oral administration form is a syrup, pill, tablet, troche, capsule, or patch.

[0006] Another example of the disclosure provides a norepinephrine reuptake inhibitor for use in treating a condition associated with pharyngeal airway collapse.

[0007] Another example of the disclosure provides the use of a norepinephrine reuptake inhibitor in treating a condition associated with pharyngeal airway collapse.

[0008] Another example of the disclosure provides the use of a norepinephrine reuptake inhibitor for the manufacture of a medicament for treating a condition associated with pharyngeal airway collapse.

[0009] 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.

[0010] 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

[0011] The following figures are provided by way of example and are not intended to limit the scope of the claimed invention.

[0012] 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.

[0013] FIGs. 2A and 2B are individual and group data showing the effect of placebo and reboxetine on AHI (4% definition for hypopneas) in 16 individuals with a previous diagnosis of OSA. Group data show medians and interquartile range. Placebo and reboxetine were administered approximately 1 week apart in random order for 1 night during a double-blinded crossover trial.

DETAILED DESCRIPTION

[0014] 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

WHAT IS CLAIMED IS:

1. Use of a norepinephrine reuptake inhibitor (NRI) in the manufacture of a medicament for treating a subject having a condition associated with pharyngeal airway collapse, wherein the NRI is to be administered in the absence of an antimuscarinic therapy.

2. The use of claim 1, wherein the NRI is to be administered as a monotherapy.

3. The use of claim 1 or 2, wherein the NRI is reboxetine or a pharmaceutically acceptable salt thereof.

4. The use of claim 3, wherein the reboxetine or pharmaceutically acceptable salt thereof is to be administered at a dosage of from about 1 mg to about 8 mg.

5. The use of claim 4, wherein the reboxetine or pharmaceutically acceptable salt thereof is to be administered at a dosage of from about 2 mg to about 6 mg.

6. The use of claim 1 or 2, wherein the NRI is edivoxetine or a pharmaceutically acceptable salt thereof.

7. The use of claim 6, wherein the edivoxetine or pharmaceutically acceptable salt thereof is to be administered at a dosage of from about 6 mg to about 36 mg.

8. The use of claim 1 or 2, wherein the NRI is viloxazine or a pharmaceutically acceptable salt thereof.

9. The use of claim 8, wherein the viloxazine or pharmaceutically acceptable salt thereof is to be administered at a dosage of from about 50 mg to about 800 mg.

10. The use of claim 1, wherein the NRI is edivoxetine or a pharmaceutically acceptable salt thereof, wherein trazodone or a pharmaceutically acceptable salt thereof is to be further administered to the subject.

11. The use of claim 1, wherein the NRI is viloxazine or a pharmaceutically acceptable salt thereof, and wherein trazodone or a pharmaceutically acceptable salt thereof is to be further administered to the subject.

12. The use of any one of claims 1-11, wherein the NRI is to be administered daily.

13. The use of any one of claims 1-12, wherein the NRI is to be administered in an oral administration form.

14. The use of claim 13, wherein the oral administration form is a syrup, pill, tablet, troche, or capsule.

15. The use of any one of claims 1-5, wherein the NRI is (S,S)-reboxetine or a pharmaceutically acceptable salt thereof.

16. The use of any one of claims 1-15, wherein the condition associated with pharyngeal airway collapse is sleep apnea.

17. The use of claim 16, wherein the condition associated with pharyngeal airway collapse is obstructive sleep apnea (OSA).

18. The use of any one of claims 1-15, wherein the condition associated with pharyngeal airway collapse is snoring.

19. The use of claim 18, wherein the condition associated with pharyngeal airway collapse is simple snoring.

20. The use of any one of claims 1-19, wherein the subject is in a non-fully conscious state.

21. The use of claim 20, wherein the non-fully conscious state is sleep.

22. A pharmaceutical composition comprising (i) edivoxetine or a pharmaceutically acceptable salt thereof, (ii) trazodone or a pharmaceutically acceptable salt thereof, and (ii) a pharmaceutically acceptable excipient or carrier.

23. A pharmaceutical composition comprising (i) viloxazine or a pharmaceutically acceptable salt thereof, (ii) trazodone or a pharmaceutically acceptable salt thereof, and (ii) a pharmaceutically acceptable excipient or carrier.

24. Use of edivoxetine or a pharmaceutically acceptable salt thereof, and trazodone or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a condition associated with pharyngeal airway collapse.

25. Use of viloxazine or a pharmaceutically acceptable salt thereof, and trazodone or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a condition associated with pharyngeal airway collapse.

26. The use of claim 24 or 25, wherein the condition associated with pharyngeal airway collapse is obstructive sleep apnea.

27. The use of any one of claims 8, 9, 11, 25 or 26, wherein the viloxazine or pharmaceutically acceptable salt thereof is present as a single enantiomer.

28. The use of claim 27, wherein the single enantiomer is (S)-viloxazine or a pharmaceutically acceptable salt thereof.

29. The pharmaceutical composition of claim 23, wherein the viloxazine or pharmaceutically acceptable salt thereof is present as a single enantiomer.

30. The use of claim 26, wherein the single enantiomer is (S)-viloxazine or a pharmaceutically acceptable salt thereof.