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Effect of Venlafaxine on Apnea-Hypopnea Index in Patients With Sleep Apnea

A Randomized, Double-Blind Crossover Study



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BACKGROUND: One of the key mechanisms underlying OSA is reduced pharyngeal muscle tone during sleep. Data suggest that pharmacologic augmentation of central serotonergic/adrenergic tone increases pharyngeal muscle tone.

RESEARCH QUESTION: We hypothesized that venlafaxine, a serotonin-norepinephrine reuptake inhibitor, would improve OSA severity.

STUDY DESIGN AND METHODS: In this mechanistic, randomized, double-blind, placebo-controlled crossover trial, 20 patients with OSA underwent two overnight polysomnograms ≥ 4 days apart, receiving either 50 mg of immediate-release venlafaxine or placebo before bedtime. Primary outcomes were the apnea-hypopnea index (AHI) and peripheral oxygen saturation (SpO₂) nadir, and secondary outcomes included sleep parameters and pathophysiologic traits with a view toward understanding the impact of venlafaxine on mechanisms underlying OSA.

RESULTS: Overall, there was no significant difference between venlafaxine and placebo regarding AHI (mean reduction, -5.6 events/h [95% CI, -12.0 to 0.9]; $P = .09$) or SpO₂ nadir (median increase, $+1.0\%$ [-0.5 to 5]; $P = .11$). Venlafaxine reduced total sleep time, sleep efficiency, and rapid eye movement (REM) sleep, while increasing non-REM stage 1 sleep ($P_{\text{all}} < .05$). On the basis of exploratory post hoc analyses venlafaxine decreased (“improved”) the ventilatory response to arousal (-30% ; $P = .049$) and lowered (“worsened”) the predicted arousal threshold (-13% ; [$P = .02$]; ie, more arousable), with no effects on other pathophysiologic traits ($P_{\text{all}} \geq .3$). Post hoc analyses further suggested effect modification by arousal threshold ($P = .002$): AHI improved by 19% in patients with a high arousal threshold (-10.9 events/h [-3.9 to -17.9]) but tended to increase in patients with a low arousal threshold ($+7$ events/h [-2.0 to 16]). Other predictors of response were elevated AHI and less collapsible upper airway anatomy at baseline ($|r| > 0.5$, $P \leq .02$).

INTERPRETATION: In unselected patients, venlafaxine simultaneously worsened and improved various pathophysiologic traits, resulting in a zero net effect. Careful patient selection based on pathophysiologic traits, or combination therapy with drugs countering its alerting effects, may produce a more robust response.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT02714400; URL: www.clinicaltrials.gov.

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KEY WORDS: lung; OSA; pharmacotherapy; pharyngeal muscle tone; venlafaxine

ABBREVIATIONS: AHI = apnea hypopnea index; ArTH = arousal threshold; NREM = nonrapid eye movement; PSG = polysomnogram; REM = rapid eye movement

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OSA is characterized by a repetitive collapse of the upper airway at night, which affects at least 10% of the US population and has been associated with various adverse health outcomes.¹⁻³ The standard of care is CPAP,⁴ but many patients are unable to tolerate this therapy long-term.⁵⁻⁸ Thus, over the past three decades various pharmacologic treatments have been evaluated as alternative options, but so far results have been mixed.⁹

One of the key goals of pharmacologic interventions for OSA has been to augment pharyngeal muscle tone during sleep: during wakefulness patients with OSA maintain airway patency via increased pharyngeal muscle tone compared with control subjects.¹⁰ However, central activation of the pharyngeal muscles is state-

specific, and in patients with OSA muscle tone drops both rapidly and substantially during the wake-sleep transition; this can contribute to the development of apneas and hypopneas.¹¹ Initially it was thought that this change in activity was due primarily to a drop in serotonergic input to the hypoglossal motoneurons.^{12,13} Therefore, several studies tried to mitigate OSA by raising serotonin levels (eg, with selective serotonin reuptake inhibitors),¹⁴⁻¹⁶ but overall success has been limited. More recent data suggest that a drop in noradrenaline levels may play a key role as well.¹⁷⁻¹⁹ Therefore, we tested the hypothesis that venlafaxine (a serotonin-norepinephrine reuptake inhibitor) improves OSA severity.

Methods

Study Design

We conducted a mechanistic, randomized, double-blind, placebo-controlled crossover study.²⁰ All participants underwent two in-laboratory overnight polysomnograms (PSGs) at least 4 days apart, based on the pharmacologic half-lives of venlafaxine and O-desmethylvenlafaxine (the only major active metabolite; $t_{1/2} = 5 \pm 2$ and 11 ± 2 h, respectively).^{21,22} Given the lack of prior data on venlafaxine in patients with OSA and consistent with other studies^{18,23} we chose a priori a single-night design to increase feasibility and to minimize risks to participants. This single-night design precluded gradual up-titration of venlafaxine. Thus, during the two study visits subjects received either 50 mg of venlafaxine (based on the usual adult starting dose range of 37.5-75 mg²¹) or an indistinguishable placebo 1 h before sleep. The allocation sequence was generated by one investigator (R. J.), using an online random sequence generator (random.org). All subjects, investigators interacting with participants, and outcome assessors were blinded to subjects' allocation sequence until the analysis stage.

Power Calculation

We estimated that a sample size of 20 subjects will provide a power > 0.8 to detect a change in apnea-hypopnea index (AHI) of 10 (± 15) events/h with an α level of 0.05.

Participants

Patients were eligible for the study if they were 18 to 70 years of age. All subjects had a history of untreated OSA with an AHI greater than 5 events/h and were recruited from the University of California San Diego sleep clinic. Exclusion criteria included the presence of pulmonary, cardiac, neurologic, or other active severe medical or psychiatric diseases; or current use of CPAP therapy. No drugs that might interact with the investigational medication or known to affect sleep were taken during the trial or 1 month before the study. We also excluded patients with known allergy to venlafaxine, currently smoking, or taking alcohol (> 3 oz/d). Written informed consent was provided by each subject before participation in the study, and the study protocol was approved by the Human Research Committee, University of California San Diego (IRB#141272).

Polysomnograms

EEGs, electro-oculograms, and surface electromyograms were applied to score arousals, leg movements, and sleep stage. Abdominal and chest movements (magnetometers), pulse oxygen saturation, and oral and nasal flow were recorded to detect respiratory events. Participants were instructed to sleep supine as much as possible throughout the duration of the night, and position was recorded on the basis of visual inspection via an infrared camera system. A registered polysomnographic technologist, who was blinded to the allocation sequence, scored the PSGs according to the Chicago criteria (ie, hypopneas were defined as a > 50% decrease in airflow, or a $\leq 50\%$ reduction in airflow associated with an oxygen desaturation of $\geq 3\%$ or arousal).²⁴

Endotype Measurements

OSA is a multifactorial disease caused by the interplay of an anatomical predisposition and several nonanatomical physiologic traits or endotypes.²⁵⁻²⁷ A detailed discussion of these endotypes and their various implications can be found in the literature,²⁸ and e-Appendix 1 and e-Figures 1 and 2 in the online article provide details of how endotypes can be quantified. In brief, based on a validated custom algorithm analyzing routine PSG data (MATLAB; MathWorks)^{27,29} we quantified the following traits for each subject

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Drs Schmickl and Li contributed equally to this manuscript.

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off CPAP during the venlafaxine vs placebo night as a percentage of eupneic ventilation/drive (Veupnea):

- Anatomical upper airway collapsibility (V_{passive} : Ventilation when upper airway dilator muscles are hypotonic/passive; higher % Veupnea values correspond with a stiffer airway).
- Pharyngeal muscle recruitment (V_{active} : Ventilation when upper airway dilator muscles are maximally activated; higher % Veupnea values indicate more muscle recruitment in response to accumulating respiratory stimuli during partial airway collapse).
- Ventilatory instability (loop gain in response to 1 disturbance/min [LG1]: this metric is dimensionless; larger values reflect greater instability, and values > 1 correspond with periodic breathing/central sleep apnea).
- Respiratory arousal threshold (ArTH: respiratory drive that causes arousal from sleep; when the airway narrows then ventilation drops while ventilatory drive rises; thus, larger % Veupnea values correspond with greater drops in ventilation that can be sustained before arousal from sleep occurs).
- Ventilatory response to arousal (amount of ventilatory overshoot during an arousal that is not explained by the respiratory drive at the time of arousal; greater values reflect a greater ventilatory overshoot, which can exacerbate ventilatory instability; see Discussion).²⁶

Furthermore, we calculated the upper airway gain, which is a function of both pharyngeal muscle recruitment and the ArTH (dimensionless; larger values indicate a greater ability to dilate pharyngeal muscles before respiratory arousals).

Results

Six of the 26 subjects screened did not meet inclusion criteria; 20 patients were randomized and completed the study (Fig 1³³). Two subjects reported mild nausea shortly after venlafaxine administration, which resolved within 1 h. In addition, one subject complained of nausea in the morning after placebo administration. No serious or unanticipated problems related to venlafaxine were observed during the study.

As shown in Table 1, subjects were middle-aged, overweight to obese, with Epworth Sleepiness Scale scores ranging clinically from no to severe sleepiness. Thirty percent of the subjects were women and 25% were nonwhite. Of note, there was no difference in BMI, percentage of time slept supine, or percentage of “first night” in the laboratory between the venlafaxine vs placebo nights ($P_{\text{all}} > .2$; e-Table 1).

Effect of Venlafaxine on Sleep

Venlafaxine vs placebo significantly decreased total sleep time, sleep efficiency, and percentage of rapid eye movement (REM) sleep but increased the percentage of non-REM (NREM) stage 1 sleep (Table 2). REM sleep was absent in seven subjects (35%) receiving venlafaxine and two subjects receiving placebo (10%).

In addition to quantifying the ArTH on the basis of analysis of the raw PSG data (“measured” ArTH), we also calculated the “predicted” ArTH on the basis of a validated clinical score incorporating age, sex, BMI, AHI, peripheral oxygen saturation (SpO_2) nadir, and the percentage of hypopneas.^{30,31} The predicted ArTH provides an estimate of the negative epiglottic pressure swing preceding arousal in $-\text{cm H}_2\text{O}$; for simplicity we used the absolute value ($\text{cm H}_2\text{O}$) for all analyses.

Statistical Analysis

Statistical analyses were performed with R (version 3.6.1).³² In preparation for each analysis we assessed normality, using a Shapiro-Wilk test in combination with histogram inspection to determine the need for nonparametric testing. Thus, as appropriate, we compared outcome data on venlafaxine vs placebo using paired t tests or Wilcoxon signed ranks tests, explored correlations between baseline characteristics and changes in AHI using Pearson or Spearman correlation coefficients, performed exploratory subgroup analyses (comparing AHI changes stratified by OSA severity and low vs high ArTH), and compared responder (arbitrarily defined as AHI-reduction by > 10 events/h) vs nonresponder characteristics using two-sample t tests. Data were summarized accordingly as mean (SD) or median (interquartile range). Statistical significance was set at $P < .05$. Comparisons of AHI, SpO_2 nadir, loop gain, ArTH, and sleep parameters were prespecified; all other analyses were performed post hoc and considered exploratory (ie, no adjustment for multiple comparisons).

Effect of Venlafaxine on OSA Severity

Overall, there was no significant difference between venlafaxine and placebo regarding AHI (mean reduction, -5.6 events/h [95% CI, -12.0 to 0.9]; $P = .09$) or SpO_2 nadir (median increase, $+1.0\%$ [-0.5 to 5]; $P = .11$) (e-Fig 3). However, individual response to venlafaxine appeared to be heterogeneous: the AHI decreased by > 10 events/h in one-third of subjects ($n = 7$; 35%), whereas in one subject (5%) the AHI increased by > 10 events/h (Fig 2). Thus, we sought to explore potential subgroups of patients who may respond to venlafaxine.

On the basis of post hoc analyses, there was no change in REM-sleep AHI ($+1.9$ events/h, $n = 11$; $P = .8$), and thus any improvement in total AHI appeared to be due primarily to changes in NREM-sleep AHI (-5.0 events/h; $P = .14$) (Table 3). Allocation order did not modify the effect of venlafaxine on the AHI ($P = .3$) (e-Table 2).

Effect of Venlafaxine on Pathophysiologic Traits

As shown in Table 4, venlafaxine vs placebo decreased the ventilatory response to arousal by 30% (-6.9% Veupnea; $P = .049$) and lowered the predicted ArTH by 13% (-2.4 $\text{cm H}_2\text{O}$; $P = .02$). There was no significant change in any of the other traits including

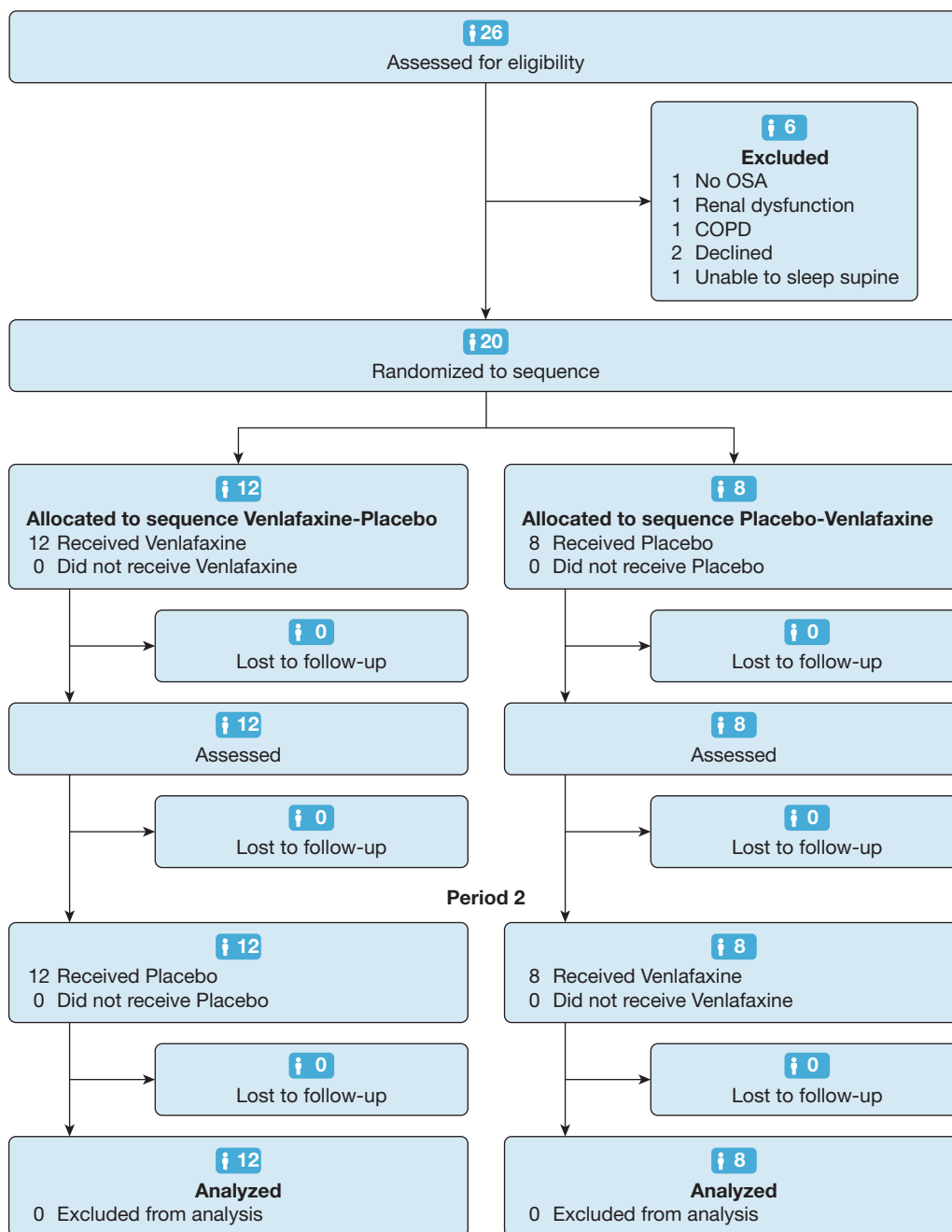


Figure 1 – CONSORT flow diagram (for crossover trials). CONSORT = Consolidating Standards of Reporting Trials. (Reprinted with permission from Dwan et al.³³)

measures of pharyngeal muscle response, loop gain, or the ArTH quantified from raw PSG signals.

Both reductions in ventilatory response to arousal ($r_s = 0.47, P = .045$) (e-Table 3) and reductions in ArTH correlated with improvements in AHI (measured ArTH: $r_s = 0.68, P = .002$; predicted ArTH: $r_p = 0.75, P < .001$) (e-Table 3).

Baseline Characteristics Predicting Response

Elevated AHI, higher respiratory ArTH (ie, harder to arouse), and higher V_{passive} (less collapsible upper airway) at baseline correlated with greater improvements in AHI on venlafaxine vs placebo ($|r| > 0.48, P < .05$) (Table 5). Similarly, responders (AHI improvement > 10 events/h) vs nonresponders

TABLE 1] Baseline Demographics

Demographic	Mean/Median (SD/IQR) or Percent (No.)	Range
Age, y	53.8 (8.1)	35-64
Sex, female	30 (6)	...
Race		
White	75 (15)	...
Black	10 (2)	...
Asian	15 (3)	...
Epworth Sleepiness Scale	8 (6-15)	4-22
Pittsburgh Sleep Quality Index	8.6 (3.3)	4-15
BMI, kg/m ²	30.9 (3.9)	24.8-39.5
Neck circumference, cm	42.3 (7.5)	34.5-63
Time between studies, d	7 (7-15)	4-22

IQR = interquartile range.

had a higher baseline AHI ($P = .04$) and tended to have a higher ArTH ($P = .07$) (e-Table 4).

Baseline AHI and predicted ArTH were highly collinear ($r_s = 0.78$, $P = 10^{-4}$), precluding a meaningful comparison of their relative predictive value via multivariable regression. On the basis of exploratory post hoc subgroup analyses (using standard cutoffs), venlafaxine improved the AHI in subjects with a high ArTH (≥ 15 cm H₂O, ie, hard to arouse) but tended to worsen the AHI in those with a low ArTH (Fig 3). Similarly, venlafaxine vs placebo improved the AHI in those with severe OSA (AHI ≥ 30 events/h) but tended

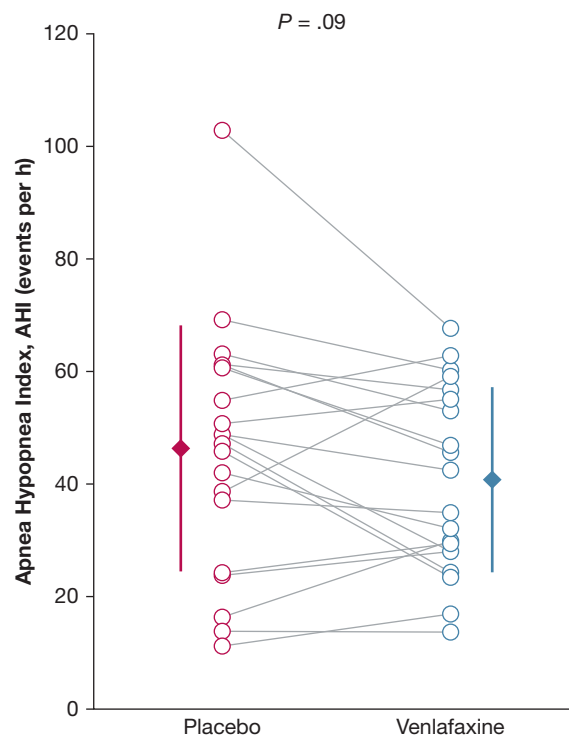


Figure 2 – Changes in apnea-hypopnea index (AHI, events/h) with venlafaxine vs placebo. Diamonds and bars show mean and SD for each condition (red, placebo; blue, venlafaxine). Circles denote individuals' AHI.

to worsen the AHI in patients with mild/moderate OSA. This finding may reflect the low ArTH in most patients with mild/moderate OSA; however, the number of subjects with mild/moderate OSA was small, precluding firm conclusions. Results were similar when dichotomizing baseline ArTH and AHI using the mean of treatment and placebo values (e-Fig 4), and thus these findings were not explained by regression to the mean.

TABLE 2] Sleep Parameters During Placebo vs Venlafaxine Night: n = 20

Sleep Parameter	Placebo	Venlafaxine	Δ Venlafaxine-Placebo	P Value
	[Mean (SD) or Median (IQR)]	[Mean (SD) or Median (IQR)]	[MD ^a (95% CI)]	
TST, min	334.6 (79.9)	284.4 (81.5)	-50.0 (-91.4 to -8.6)	.02 ^b
Sleep efficiency, %	72.5 (15.5)	63.1 (16.7)	-9.4 (-17.9 to -1)	.03 ^b
Sleep onset latency, min	4.2 (1.5-11.2)	5.0 (3.0-18.1)	1.5 (-0.7 to 21.5)	.09
Total arousal index, h ⁻¹	39.3 (17.8)	44.2 (16.5)	4.9 (-3.8 to 13.6)	.3
NREM stage 1 sleep, % TST	23.9 (16.6-29.4)	39.0 (29.6-45.2)	12.1 (2.4 to 20.6)	.02 ^b
NREM stage 2 sleep, % TST	54.4 (13.3)	53.2 (11.8)	-1.2 (-8.3 to 5.9)	.7
NREM stage 3 sleep, % TST	7.5 (7.2)	5.2 (7.0)	-2.3 (-5.6 to 0.9)	.2
REM sleep, % TST	10.8 (7.8)	4.2 (5.9)	-6.6 (-11.6 to -1.6)	.01 ^b

Δ = change; MD = mean or median of differences for normally or nonnormally distributed differences, respectively; NREM = nonrapid eye movement; REM = rapid eye movement; TST = total sleep time. See Table 1 legend for expansion of other abbreviation.

^aThe median of differences is mathematically not necessarily the same as the difference of medians; here the median of differences is the more informative measure as it takes into account the paired nature of the data shown.

^b $P < .05$.

TABLE 3] Sleep Apnea Severity on Venlafaxine vs Placebo

Sleep Apnea Measure	Placebo	Venlafaxine	Δ Venlafaxine-Placebo	No. ^a	P Value
	[Mean (SD) or Median (IQR)]	[Mean (SD) or Median (IQR)]	[MD (95% CI)]		
AHI, events/h					
Total	46.1 (21.9)	40.5 (16.5)	-5.6 (-12.0 to 0.9)09
By sleep stage					
NREM	45.1 (22.7)	40.1 (16.3)	-5.0 (-11.8 to 1.8)14
REM	47.1 (17.2)	48.9 (22.2)	1.9 (-15.9 to 19.6)	11	.8
By time of night					
NREM AHI, first half of night	44.4 (26.2)	35.6 (21.1)	-8.8 (-18.7 to 1.1)08
NREM AHI, second half of night	45.7 (21.5)	44.6 (14.7)	-1.1 (-8.7 to 6.5)8
By event type					
Obstructive apnea index	17.7 (12.7)	15.3 (13.1)	-2.5 (-6.9 to 2.0)3
Central apnea index	1.1 (0.3 to 2.4)	0.3 (0 to 2.8)	-0.6 (-3.3 to -0.1)02 ^b
Mixed apnea index	0.2 (0 to 3.7)	0.2 (0 to 1.3)	0 (-3.8 to 0.6)	...	1
Hypopnea index	21.2 (9.7)	20.6 (11.2)	-0.5 (-4.5 to 3.4)8
O₂ Saturation, %					
Nadir	81.5 (75.8 to 84.2)	82.0 (80.0 to 84.0)	1.0 (-0.5 to 5)11
Mean	92.7 (1.6)	92.5 (1.4)	-0.2 (-0.9 to 0.5)6

AHI = apnea-hypopnea index. See Table 1 and 2 legends for expansion of other abbreviations.

^an = 20 unless stated otherwise.

^bP < .05.

Discussion

We note three key findings: (1) Overall, a single 50-mg dose of venlafaxine did not significantly improve the AHI, but individual responses appeared variable; (2) baseline ArTH and AHI predicted treatment response; and (3) counter to our expectation, we failed to detect an improvement in muscle recruitment. Instead,

exploratory analyses suggest that venlafaxine lowered the ventilatory response to arousal and the ArTH. On the basis of the current pathophysiologic model of OSA these changes are expected to improve and worsen OSA severity, respectively, potentially explaining the zero net effect on the AHI overall and the differential response based on subjects' baseline ArTH.

TABLE 4] Changes in Endotypes With Venlafaxine vs Placebo

Endotype	Placebo	Venlafaxine	Δ Venlafaxine-Placebo	n	P Value
	[Mean (SD) or Median (IQR)]	[Mean (SD) or Median (IQR)]	[MD (95% CI)]		
V _{passive} , %V _{eupnea}	95.0 (86.1 to 97.3)	97.2 (91.6 to 98.1)	0.5 (-3.5 to 6.3)	19	.4
V _{active} , %V _{eupnea}	96.1 (82.4 to 102.5)	101.7 (92.0 to 103.8)	-0.9 (-16.6 to 4.9)	19	.7
UAG, dimensionless	0.02 (-0.12 to 0.69)	0.43 (0.06 to 0.6)	0.25 (-0.14 to 0.58)	19	.3
Loop gain 1, dimensionless	0.56 (0.14)	0.58 (0.15)	0.01 (-0.05 to 0.07)	19	.7
Loop gain n, dimensionless	0.39 (0.12)	0.37 (0.09)	-0.02 (-0.07 to 0.03)	19	.4
Arousal threshold (ArTH), %V _{eupnea}	118.6 (113.4 to 137.9)	115.6 (108.2 to 130.8)	-3.1 (-10.7 to 6.5)	19	.6
Predicted ArTH, cm H ₂ O	18.4 (6.5)	16.0 (5.8)	-2.4 (-4.3 to -0.5)	20	.02 ^a
VRA, %V _{eupnea}	23.2 (14.0 to 32.9)	14.2 (3.6 to 19.6)	-6.9 (-14.6 to -0.1)	19	.049 ^a

ArTH = respiratory arousal threshold; UAG = upper airway gain; V_{active} = ventilation when upper airway dilator muscles are maximally activated; V_{eupnea} = eupneic ventilation; V_{passive} = ventilation when upper airway dilator muscles are hypotonic/passive; VRA = ventilatory response to arousal. See Table 1 and 2 legends for expansion of other abbreviations.

^aP < .05.

TABLE 5] Predictors of Response: Correlations Between Baseline Characteristics and Change in Apnea-Hypopnea Index^a

Baseline Characteristic (ie, Measured on Placebo)	r_p/r_s (95% CI)	Type ^b	n	P Value
Age, y	-0.23 (-0.6 to 0.2)	P	20	.3
Epworth Sleepiness Scale score	0.07 (-0.4 to 0.5)	S	20	.8
AHI, events/h	-0.66 (-0.9 to -0.3)	P	20	.002 ^c
V _{passive} , %Veupnea	0.52 (0.1 to 0.8)	S	19	.02 ^c
V _{active} , %Veupnea	0.16 (-0.3 to 0.6)	S	19	.5
UAG, dimensionless	0.02 (-0.4 to 0.5)	P	19	1
Loop gain 1, dimensionless	-0.28 (-0.7 to 0.2)	P	19	.2
ArTH, %Veupnea	-0.48 (-0.8 to -0.03)	S	19	.04 ^c
Predicted ArTH, cm H ₂ O	-0.53 (-0.8 to -0.1)	P	20	.02 ^c
VRA, %Veupnea	-0.14 (-0.6 to 0.3)	S	19	.6

See Table 1, 2, and 4 legends for expansion of abbreviations.

^aMore negative AHI_{venlafaxine-placebo} values reflect greater improvement in AHI. Higher baseline AHI and higher baseline ArTH (ie, being hard to arouse) were significantly correlated with more pronounced improvements in AHI on venlafaxine.

^bType denotes Pearson (P) vs Spearman (S) for normally vs nonnormally distributed variables, respectively.

^c $P < .05$.

After a mechanical collapse of the upper airway, accumulation of respiratory stimuli (ie, rise in intrapharyngeal negative pressure plus CO₂) leads to a gradual activation of pharyngeal muscles; if sleep is maintained until airway patency is restored (high ArTH) then the result is stable breathing, but if the person arouses before airway opening (low ArTH) then repetitive cycles of airway collapse and arousals (ie, OSA) are expected.^{34,35} On the basis of indirect evidence from other studies, we expected that serotonergic/

noradrenergic augmentation by venlafaxine would increase pharyngeal muscle activity^{14,23,36} while lowering the ArTH.^{18,23} As expected, venlafaxine lowered the ArTH predicted on the basis of a clinical score (and shifted sleep toward lighter stages); however, for unclear reasons we failed to detect a change in the ArTH estimated from PSG data using a custom algorithm, and did not find a change in pharyngeal muscle recruitment using the same methodology. Interestingly, exploratory analyses suggested that venlafaxine blunts the

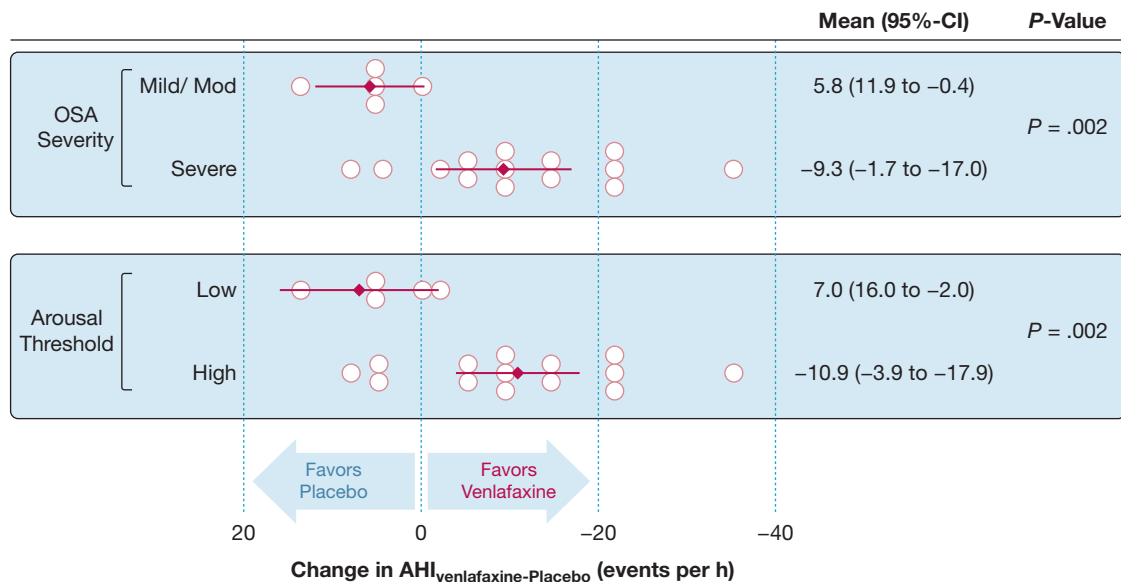


Figure 3 – Change in AHI with venlafaxine vs placebo stratified by OSA severity and the predicted arousal threshold, using standard cutoffs. Diamonds and bars show mean and 95% CI for each group; red circles denote individuals' change in AHI. See Figure 2 legend for expansion of abbreviation.

ventilatory response to arousal. During partial airway obstruction accumulation of respiratory stimuli gradually increases respiratory drive. Thus, when pharyngeal dilators restore airway patency, ventilation rises temporarily to levels in excess of baseline ventilation. This excess ventilation is greatly increased when the airway reopening is associated with a cortical arousal (267% vs 180% prehypopnea baseline; $P < 10^{-10}$), which may exacerbate the subsequent drop in respiratory drive and pharyngeal muscle activation, thus potentially triggering repetitive cycles of airway collapse and arousals (ie, OSA).³⁴ Our findings are intriguing for two reasons: First, whereas results from previous studies have been mixed,^{26,37,38} our findings provide further support for ventilatory response to arousal being an independent and important pathophysiologic mechanism underlying OSA in some patients. Second, aside from acetazolamide,²⁶ venlafaxine is the only drug that has been shown to lower ventilatory response to arousal, which may have important implications for a personalized, multimodal therapy approach in the future.³⁹

To our knowledge this is the first study assessing the effect of venlafaxine on OSA. However, several studies evaluated pharmacodynamically similar medications: two small randomized controlled trials assessed protriptyline, a tricyclic antidepressant with noradrenergic, serotonergic, and some anticholinergic effects. One of these studies found no overall effect on the AHI but noted substantial interindividual variability,⁴⁰ and the other reported a small reduction in OSA severity due to a reduction in REM sleep.⁴¹ Neither of these studies assessed effects on the pathophysiologic traits, making comparisons difficult. Similarly, a study of clonidine (α_2 -agonist with sympatholytic effects) reported minor improvements in OSA severity primarily due to a reduction in REM sleep.⁴² In addition, in a study of healthy subjects,⁴³ clonidine reduced (central) hypocapnic ventilatory response (a component of loop gain), thus lowering the propensity to central apneas (lower apnea threshold, higher CO₂ reserve). In contrast, in our study venlafaxine did not affect loop gain, suggesting that these two drugs have different effects on control of breathing. Further, in a small crossover trial the potent noradrenaline-reuptake inhibitor atomoxetine alone lowered the ArTH with a zero net effect on the AHI, but coadministration of the anticholinergic oxybutynin mitigated its effect on the ArTH⁴⁴ (and possibly augmented pharyngeal muscle tone in REM),⁴⁵⁻⁴⁸ resulting in a large improvement in

OSA severity by ~70%.¹⁸ Moreover, a crossover trial testing the effect of single-dose desipramine (a tricyclic antidepressant with potent noradrenergic, some serotonergic and mild anticholinergic properties) in 14 patients with OSA showed many similar findings as in our study, including a shift toward lighter sleep stages, significant lowering of the ArTH, and a nonsignificant reduction of overall AHI by 18%, with about one-third of patients being classified as responders (drop in AHI by >20 events/h).²³ Unfortunately, neither of these trials measured ventilatory response to arousal. However, these data support the notion that drugs increasing noradrenergic tone have opposing effects on the underlying OSA traits, resulting in a small to zero net effect (and high interindividual variability) when used alone, but combination with agents increasing the ArTH (eg, eszopiclone³⁵) may produce synergistic effects that may result in more robust responses and substantially improved OSA severity.

Strengths and Limitations

Strengths of our study include the use of a randomized, double-blind, placebo-controlled trial design, which makes selection or measurement biases unlikely, and detailed physiologic assessments providing mechanistic insights. Limitations include the lack of “gold standard” assessment of pathophysiologic traits, which may have reduced our ability to detect changes in muscle tone. Also, although the predicted ArTH has been validated as a measure of interindividual baseline ArTHs, it has not been validated as a way to estimate changes in intraindividual ArTHs. Further, given the risk of chance findings, the results from our post hoc analyses do not allow firm conclusions but may be valuable for hypothesis generation guiding future research: for example, any potential beneficial effects of venlafaxine on the NREM-AHI tended to occur only during the first half of the night, which may be due to sleep stage effects (more deep sleep with high ArTH during the first vs second half of the night) or pharmacokinetic reasons (ie, drop in concentration below therapeutic levels over time). Thus, future research should consider use of extended-release formulations, longer durations of administration, and/or higher doses. Such research will also help address another important limitation of our study: the pharmacokinetic effects of a single 50-mg dose of immediate-release venlafaxine on serotonergic/noradrenergic tone are difficult to predict and were not measured: chronic administration of low-dose venlafaxine (50-75 mg) is sufficient to achieve in vivo the

same level of serotonin transporter occupancy (?80%) as with high-dose venlafaxine,^{49,50} but blocks only about 10% to 30% of norepinephrine transporters vs 30% to 60% with doses > 150 mg.⁵¹ This dose-dependent effect has also been corroborated by studies using functional assessments.^{52,53} Moreover, many effects of antidepressants are mediated by adaptive changes related to chronic (> 2-6 weeks) administration.⁵⁴ Thus, our results may reflect more changes in serotonergic than noradrenergic tone, and the effects of venlafaxine on OSA may be quite different when administered in higher doses and/or long-term. Another limitation is that some of the changes in AHI as well as changes in endotypes were likely mediated by shifts in sleep stages. Moreover, in this study reductions in ArTH correlated with improvements in AHI (e-Table 3); this is in contrast to the current pathophysiologic model of OSA, which predicts that lowering the ArTH causes worsening OSA (e-Appendix 1, e-Figs 1, 2). This association may be explained by the observation that only subjects with a high baseline ArTH (hard to wake) were able to “tolerate” the alerting effects of venlafaxine

and benefit from its effect on ventilatory response to arousal (ie, had improvements in AHI despite reductions in ArTH); conversely, in subjects with a low baseline ArTH (easy to wake) the potential magnitude of ArTH reductions is relatively limited, but the effects on the ventilatory response to arousal, resulting in the observed zero effect on AHI in this subgroup. To test this hypothesis future studies combining venlafaxine with drugs that increase the ArTH are warranted.

Interpretation

Overall, a single dose of venlafaxine had no significant effect on the AHI, but worsened sleep architecture. There may be subgroups of patients defined by physiologic traits in whom venlafaxine may have future clinical value, and combination with drugs improving sleep continuity may result in synergistic effects. Pharmacotherapy for OSA may be achievable, but patient-centered outcomes (eg, sleepiness) will need to be assessed in rigorous multicenter trials.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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