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Trazodone Increases the Respiratory Arousal Threshold in Patients with Obstructive Sleep Apnea and a Low Arousal Threshold

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Study Objectives: The effect of common sedatives on upper airway physiology and breathing during sleep in obstructive sleep apnea (OSA) has been minimally studied. Conceptually, certain sedatives may worsen OSA in some patients. However, sleep and breathing could improve with certain sedatives in patients with OSA with a low respiratory arousal threshold. This study aimed to test the hypothesis that trazodone increases the respiratory arousal threshold in patients with OSA and a low arousal threshold. Secondary aims were to examine the effects of trazodone on upper airway dilator muscle activity, upper airway collapsibility, and breathing during sleep.

Design: Patients were studied on 4 separate nights according to a within-subjects cross-over design.

Setting: Sleep physiology laboratory.

Patients: Seven patients with OSA and a low respiratory arousal threshold.

Interventions: In-laboratory polysomnograms were obtained at baseline and after 100 mg of trazodone was administered, followed by detailed overnight physiology experiments under the same conditions. During physiology studies, continuous positive airway pressure was transiently lowered to measure arousal threshold (negative epiglottic pressure prior to arousal), dilator muscle activity (genioglossus and tensor palatini), and upper airway collapsibility (Pcrit).

Measurements and Results: Trazodone increased the respiratory arousal threshold by 32 ± 6% (-11.5 ± 1.4 versus -15.3 ± 2.2 cmH_2O, $P < 0.01$) but did not alter the apnea-hypopnea index (39 ± 12 versus 39 ± 11 events/h sleep, $P = 0.94$). Dilator muscle activity and Pcrit also did not systematically change with trazodone.

Conclusions: Trazodone increases the respiratory arousal threshold in patients with obstructive sleep apnea and a low arousal threshold without major impairment in dilator muscle activity or upper airway collapsibility. However, the magnitude of change in arousal threshold was insufficient to overcome the compromised upper airway anatomy in these patients.

Keywords: Arousal, lung, muscles, respiratory physiology, sedative, sleep-disordered breathing, upper airway

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INTRODUCTION

Obstructive sleep apnea (OSA) is an increasingly common sleep related breathing disorder.[1] OSA is characterized by the occurrence of repetitive respiratory events, each lasting > 10 sec, in which the upper airway narrows or closes restricting airflow during sleep. Termination of respiratory events is typically associated with a brief awakening from sleep (cortical arousal). In other instances, sufficient recruitment of pharyngeal dilator muscles occurs to restore airflow in the absence of cortical arousal.[2]

In addition to some degree of upper airway compromise, other nonanatomical traits importantly contribute to OSA pathogenesis in most patients with OSA.[2-7] Under some circumstances, cortical arousal likely serves as a last line of defense to assist in rapidly terminating, severe respiratory events.[2,8] However, awakening too easily to airway narrowing, i.e., having a low respiratory arousal threshold, may perpetuate breathing instability and subsequent respiratory events. Indeed, a low arousal threshold is likely to be an important nonanatomical contributor to the pathogenesis of OSA in as many as one third of all patients with OSA.[2,3,5,9]

A low respiratory arousal threshold could contribute to OSA via several mechanisms. First, repetitive cortical arousals disrupt sleep continuity and prevent deeper stages of sleep that are often associated with stable breathing.[10] Second, a brisk ventilatory response can occur with arousal, which could perpetuate fluctuations in CO_2 and lead to respiratory control instability.[5,6,11,12] Lastly, periods of breathing stability during sleep, mediated by an increase in the arousal threshold and increased pharyngeal dilator muscle activation,[13,14] occur intermittently in most patients with OSA.[4] Thus, waking up prematurely to a relatively modest level of airway narrowing can limit the ability to build up sufficient respiratory stimuli to recruit the pharyngeal dilator muscles to open the upper airway, thereby achieving breathing stability.[2,11] Importantly, if sleep could be maintained without arousal, relatively small increases in respiratory stimuli are predicted to stabilize breathing in many patients with OSA.[11,15]

Accordingly, pharmacologically increasing the threshold for cortical arousal to respiratory stimuli may facilitate breathing stability during sleep in some patients with OSA. Recent proof-of-concept clinical data provide support for this concept.[9] In considering this approach, it is important to optimize the balance between retaining the beneficial components of arousal for potential times of need (e.g., during marked hypoxemia) versus minimizing the undesirable effects of repetitive arousals to

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relatively mild episodes of airway narrowing. In addition, sedative-induced decrements in pharyngeal dilator muscle activity also could worsen apnea. Given the high rates of sedative use in the community, particularly in the obese[16], it is important to determine the effects of sedatives on upper airway physiology and breathing during sleep.

Trazodone, a serotonin antagonist and reuptake inhibitor, is the most commonly used sedative in the United States. Trazodone has been shown to reduce breathing disturbances without impairing upper airway muscle activity in an English bulldog model of OSA.[17] However, the effects of trazodone on upper airway muscle activity, airway collapsibility, and breathing during sleep in humans has not been studied. A standard dose of trazodone (100 mg) increases the arousal threshold to chemical (hypercapnia) but not mechanical (transient continuous positive airway pressure [CPAP] reductions) stimuli in unselected patients with OSA (with a wide range of arousal thresholds).[18] In the current detailed physiology study, we targeted the clinically relevant group of patients with OSA with low arousal thresholds, and hypothesized that trazodone would increase the arousal threshold to transient CPAP reductions. Secondary aims were to examine the effects of trazodone on pharyngeal dilator muscle activity and responsiveness, upper airway collapsibility, and breathing during sleep on an individual patient basis to provide mechanistic insight.

METHODS

Patients

Seven patients with OSA (1 female) who took part in a larger study investigating the multifactorial causes of OSA[3] participated in the current subprotocol. Patients who were estimated to have a low respiratory arousal threshold ($\geq$ 15 cmH_2O) following preliminary visual inspection of the epiglottic pressure swings prior to arousal during a baseline physiology night were invited to participate in the current protocol. All patients had no history of allergy or an adverse reaction to trazodone or any other sedative, had been treated with CPAP for $\geq$ 3 mo, were otherwise healthy, and were not taking any medications known to affect sleep or the other variables measured in the study. There were no other specific inclusion/exclusion criteria. OSA was defined as an apnea-hypopnea index (AHI) $\geq$ 10 events/h sleep. Each participant provided informed written consent to participate in the protocol, which was approved by the Partners HealthCare Institutional Review Board.

Measurements and Equipment

Polysomnography

Electroencephalograms, electrooculograms, and surface electromyograms (EMG) were applied to score arousals, leg movements, and stage sleep.[19,20] Abdominal and chest bands, a pulse oximeter, a position sensor, and airflow monitoring devices (nasal pressure plus thermistor) were applied to detect respiratory events according to standard criteria.[21]

Physiological Measurements

The nostrils were decongested (0.05% oxymetazoline HCl) and the clearer nostril was anesthetized (4% lidocaine HCl). An epiglottic pressure transducer (model MCP-500, Millar, Houston, TX) was advanced 1 to 2 cm below the base of the tongue. The transducer was taped to the nostril and passed through a port in a nasal CPAP mask (Gel Mask, Philips Respironics, Murrysville, PA). A pneumotachograph (model 3700A, Hans Rudolf Inc, Kansas City, MO) with a differential pressure transducer (Validyne Corporation, Northbridge, CA) in series was attached to the mask for accurate quantification of airflow. Bipolar EMG recordings of genioglossus and tensor palatini were obtained via two stainless steel fine-wire intramuscular electrodes (for each muscle) coated with Teflon (Cooner Wire Company, Chatsworth, CA). Two mm of Teflon was removed from the tip. Electrodes were inserted into the genioglossus muscle via a 25-gauge needle and into the tensor palatini at a 45° angle along the lateral surface of the medial pterygoid plate as described previously.[22] Signals were acquired on a 1401-plus interface and Spike 2 software (Cambridge Electronic Design Ltd., Cambridge, UK).

Protocol

Each patient was studied overnight on four separate occasions at least 1 w apart. The five conditions were: (1) a standard in-laboratory overnight polysomnogram off CPAP to quantify the apnea-hypopnea index (AHI) at baseline; (2) a repeat polysomnogram off CPAP following 100 mg of trazodone immediately prior to sleep; (3) a detailed baseline physiology night to quantify the respiratory arousal threshold, upper airway dilator muscle activity and responsiveness, respiratory parameters (minute ventilation, upper airway resistance, and peak flow), and the critical closing pressure of the upper airway (Pcrit); and (4) a repeat detailed physiology night after receiving 100 mg of trazodone immediately prior to sleep.

Following instrumentation during the detailed physiology studies, maneuvers including swallows and tongue protrusions were performed to determine maximal genioglossus and tensor palatini EMG.[23,24] Wakefulness upper airway muscle activity and respiratory parameters were acquired during quiet breathing on and off therapeutic CPAP prior to lights out at approximately 10:30. If required, the CPAP level was increased throughout the night to eliminate any sign of inspiratory flow limitation (according to the epiglottic pressure-flow relationship), yielding the holding pressure.

The respiratory arousal threshold, upper airway muscle responsiveness during sleep, and Pcrit were measured as described previously.[3] Briefly, during stable, supine, non-rapid eye movement (NREM) sleep, the CPAP level was transiently reduced for up to 3 min to induce varying degrees of upper airway collapse using a modified CPAP device capable of delivering $\pm$ 20 cmH_2O (Philips Respironics). Upper airway muscle activity and respiratory parameters at the CPAP holding pressure were acquired for 1 min prior to each transient CPAP reduction. The methods used to quantify these metrics are outlined below.

Data Analysis

CPAP usage was quantified objectively via a built-in compliance meter. Arousal, sleep scoring, and respiratory event detection were performed blinded to the study intervention. Raw genioglossus and tensor palatini EMG were rectified, moving-time averaged (100 ms), and expressed as a percentage of maximum activity.[23,24] Peak (maximum during inspiration) and tonic EMG (nadir during expiration), and respiratory parameters

were quantified on a breath-by-breath basis using custom-designed semi-automated software as described previously.[25] Upper airway resistance (R_{UA}) was quantified as the difference in mask versus epiglottic pressure during inspiration at a flow rate of 200 mL/s.[25] Artifact-free respiratory and upper airway EMG variables were averaged for data collection periods of at least 5 min during quiet wakefulness with and without therapeutic CPAP and for the 60 sec prior to each CPAP drop while on therapeutic CPAP during NREM sleep.

Physiology parameters derived from transient reductions in CPAP were quantified as described previously.[3] Briefly, the respiratory arousal threshold was quantified as the average nadir epiglottic pressure immediately prior to cortical arousal (> 3 sec of high-frequency activity on the EEG) for CPAP drops ≥ 10 sec combined with a ≥ 2 cmH_2O decrement in epiglottic pressure preceding arousal. Genioglossus and tensor palatini muscle responsiveness during sleep was defined as the average slope of the relationship between peak EMG and nadir epiglottic pressure derived from all artifact-free breaths during CPAP drops. To quantify Pcrit, linear regression was performed between peak inspiratory flow and mask pressure for breaths three to five after each CPAP drop in cases where the breaths were flow limited.

Statistical Procedures

Statistical comparisons between baseline and trazodone nights for polysomnography and key physiological variables were performed using Student paired *t*-tests. Analysis of variance (ANOVA) for repeated measures was used to examine trazodone, condition (wakefulness no CPAP, wakefulness on CPAP, and NREM on CPAP) and trazodone × condition interaction effects on respiratory and upper airway EMG muscle activity (SPSS version 21, SPSS Inc., Chicago, IL). Where significant ANOVA effects were observed, *post hoc* comparisons were performed using Student paired *t*-tests. Statistical significance was inferred when $P < 0.05$. All data are reported as mean ± standard error of the mean.

RESULTS

Anthropometric and Polysomnographic Characteristics

The mean age and body mass index of the participants was 45 ± 3 y (range, 31-56) and 33 ± 2 kg/m^2 (range, 25-39), respectively. Objective CPAP compliance during the 3 mo prior to the study was high at 5.9 ± 0.4 h (range, 5-8.2) per night. On average, OSA was severe (Table 1), although there was a wide range in severity between participants from 10 to 101 events per hour of sleep.

As a group, polysomnographic parameters were similar at baseline and following 100 mg of trazodone prior to sleep (Table 1). On average, the arousal index decreased following trazodone compared to baseline, but this difference was not statistically significant (P = 0.09). Average values for percent time spent in N1 sleep decreased, whereas percent N2 sleep increased (Table 1). However, these changes also were not statistically significant (P = 0.19 and P = 0.12, respectively).

Table 1—Polysomnography parameters during baseline and trazodone off continuous positive airway pressure

	Baseline	Trazodone
Apnea-hypopnea index (events/h sleep)	39 ± 12	39 ± 11
Arousal index (arousals/h of sleep)	37 ± 6	31 ± 4
Sleep efficiency (% total sleep time)	78 ± 5	76 ± 6
% Stage N1 (% total sleep time)	47 ± 9	39 ± 6
% Stage N2 (% total sleep time)	45 ± 7	52 ± 4
% REM (% total sleep time)	8 ± 2	9 ± 2
Nadir oxygen saturation (%)	82 ± 4	84 ± 3
Average oxygen saturation during sleep (%)	94 ± 2	95 ± 1

REM, rapid eye movement sleep. Values are mean ± standard error of the mean.

Physiological Variables

Respiratory variables (minute ventilation, peak flow, and upper airway resistance) and upper airway dilator muscle activity during wakefulness (on and off CPAP) and during stable NREM sleep on therapeutic CPAP during baseline and trazodone nights are displayed in Table 2. There was no significant trazodone or trazodone by condition (wakefulness no CPAP, wakefulness on CPAP, and NREM on CPAP) interaction effects for respiratory or upper airway EMG activity.

An additional 0.7 ± 0.2 cmH_2O of CPAP was applied during NREM sleep compared to the wakefulness CPAP condition during the trazodone night. Minute ventilation decreased from wakefulness off CPAP to NREM sleep on CPAP during baseline and trazodone nights. Upper airway resistance decreased with CPAP compared to without CPAP during wakefulness on both study nights. Compared to the no-CPAP wakefulness condition, peak and tonic genioglossus EMG decreased with CPAP application during wakefulness and NREM sleep during the baseline night. Similar non-significant reductions in peak (P = 0.1 and P = 0.1, respectively) and tonic (P = 0.08 and P = 0.07, respectively) genioglossus EMG were observed during the trazodone night. Tensor palatini EMG decreased on CPAP compared to off CPAP during wakefulness, with further reductions in NREM sleep during both the baseline and trazodone nights (Table 2).

A similar quantity of CPAP drops was delivered during the baseline versus the trazodone physiology night (17 ± 3 versus 20 ± 2, P = 0.18). The number of artifact-free CPAP drops and the change from the holding level during CPAP drops are displayed in Table 3. The respiratory arousal threshold increased by 3.8 ± 1 cmH_2O during NREM sleep following trazodone. This equates to a 32 ± 6% increase from baseline (Figure 1). For CPAP drops that triggered an arousal, the average time to arousal from stimulus onset was not different following trazodone compared to baseline (52 ± 11 versus 35 ± 5 sec, P = 0.23). Similarly, the nadir oxygen saturation associated with CPAP drops that triggered arousal was not different following trazodone versus baseline (88 ± 1 versus 89 ± 1%, P = 0.27). Minute ventilation and peak inspiratory flow tended to be lower on the breath immediately prior to arousal during the trazodone night compared to baseline (Table 3). However, these differences were not statistically significant (P = 0.08 and P = 0.10, respectively). Upper airway EMG activity on the breath prior to arousal was not different during trazodone compared to the baseline night (all P > 0.5) (Table 3).

Table 2—Respiratory and upper airway muscle activity during wakefulness and sleep during baseline and trazodone

	Baseline			Trazodone		
	Wakefulness		NREM	Wakefulness		NREM
	No CPAP	On CPAP	On CPAP	No CPAP	On CPAP	On CPAP
# of breaths analyzed	78 ± 10	94 ± 27	114 ± 22	65 ± 7	93 ± 33	116 ± 21
CPAP (cmH_2O)	–	9.4 ± 0.7	9.8 ± 1.0	–	9.8 ± 1.0	10.6 ± 1.1[b]
Vi (L/min)	8.5 ± 0.5	7.4 ± 0.9	6.5 ± 0.6[a]	8.5 ± 0.7	7.4 ± 1.1	6.5 ± 0.3[a]
PIF (L/s)	0.52 ± 0.04	0.54 ± 0.07	0.43 ± 0.03	0.51 ± 0.05	0.55 ± 0.07	0.46 ± 0.03
R_{UA} 200(cmH_2O/L/s)	2.0 ± 0.4	1.1 ± 0.2[a]	1.4 ± 0.3	2.7 ± 0.7	0.9 ± 0.2[a]	1.3 ± 0.3
Peak GG EMG	6.2 ± 2.5	2.9 ± 2.1[a]	1.6 ± 0.9[a]	10.6 ± 3.4	5.0 ± 2.0	5.4 ± 3.0
Tonic GG EMG	2.2 ± 0.8	0.9 ± 0.5[a]	0.5 ± 0.2[a]	4.5 ± 1.7	1.6 ± 0.8	2.0 ± 1.3
Tonic TP EMG	5.4 ± 1.6	3.5 ± 1.1[a]	0.8 ± 0.1[a,b]	4.9 ± 0.6	3.4 ± 0.4[a]	1.0 ± 0.2[a,b]

There were no significant trazodone or trazodone × condition interaction effects. [a]Denotes a significant difference compared to the equivalent No CPAP condition. [b]Denotes a significant difference compared to the equivalent On CPAP condition (wakefulness versus NREM sleep). Values are mean ± standard error of the mean. CPAP, continuous positive airway pressure; EMG, electromyographic activity; GG, genioglossus; NREM, nonrapid eye movement sleep; PIF, peak inspiratory flow; R_{UA} 200, upper airway resistance measured at a flow rate of 200 mL/s; TP, tensor palatini; Vi, minute ventilation.

Table 3—CPAP drop stimulus characteristics, respiratory, and upper airway muscle activity during the breath immediately prior to arousal

	Baseline	Trazodone
Stimulus characteristics		
Number of artifact-free CPAP drops/ patient	13 ± 3	15 ± 2
Delta CPAP (cmH_2O)	5.0 ± 0.5	5.7 ± 0.4
Respiratory and upper airway EMG characteristics for the breath prior to arousal		
Minute ventilation (L/m)	4.4 ± 0.9	2.1 ± 0.7
Inspiratory time (s)	2.3 ± 0.2	2.5 ± 0.3
Peak inspiratory flow (L/s)	0.29 ± 0.06	0.17 ± 0.05
Peak genioglossus EMG (% max)	10.3 ± 5.5	16.5 ± 11.2
Peak tensor palatini EMG (% max)	4.3 ± 1.7	3.0 ± 0.8
Tonic genioglossus EMG (% max)	3.5 ± 2.0	6.1 ± 4.1
Tonic tensor palatini EMG (% max)	2.3 ± 0.7	1.9 ± 0.4

Values are mean ± standard error of the mean. There were no statistically significant differences across conditions. CPAP, continuous positive airway pressure; EMG, electromyographic activity; max, maximum.

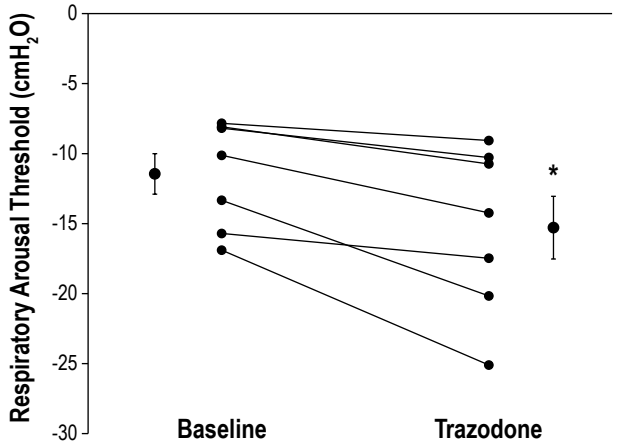

Figure 1—Respiratory arousal threshold values during baseline and following 100 mg of trazodone prior to sleep. Individual and mean ± standard error of the mean data are presented during both conditions. The asterisk denotes a significant difference between baseline and trazodone study nights.

Genioglossus and tensor palatini muscle responsiveness (%max EMG/-cmH_20) during CPAP drops were not systematically different between baseline and trazodone conditions (Figure 2A and 2B, respectively). There were insufficient flow-limited breaths for the three to five breaths post-CPAP reduction to estimate Pcrit in one patient. Of the remaining six-paired comparisons, airway collapsibility was not different during the trazodone night compared to baseline (0.2 ± 0.8 versus -0.1 ± 1.5 cmH_2O, P = 0.84).

Individual anthropometric, AHI, arousal index, arousal threshold, Pcrit, and genioglossus and tensor palatini muscle responsiveness data at baseline and following trazodone are displayed in Table 4. All participants were estimated to have a low respiratory arousal threshold (≥ 15 cmH_2O) after their baseline study. However, detailed *post hoc* analyses revealed that one participant had a slightly higher baseline value (-16.9 cmH_2O, Table 4). Three of the participants had poor genioglossus muscle responsiveness at baseline according to previously defined criteria (< 0.1% of maximum EMG increase per negative cmH_2O of epiglottic pressure).[3] Of the six participants in whom baseline Pcrit data were available, four had positive values (Table 4).

DISCUSSION

Approximately one third of patients with OSA have a low arousal threshold.[2,3,5,9] The main finding of this detailed physiology study is that, on average, 100 mg of trazodone increases the respiratory arousal threshold by more than 30% compared to baseline in patients with OSA and a low arousal threshold. Conversely, 100 mg of trazodone does not cause major reductions in upper airway dilator muscle activity/responsiveness during sleep, upper airway collapsibility (Pcrit), or breathing during sleep in patients with OSA and a low arousal threshold.

Table 4—Individual patient anthropometric, key polysomnographic, and physiology parameters during baseline versus trazodone

	BMI (kg/m^2)	Age (y)	AHI (events/h)	AI (arousals/h)	AT (cmH_2O)	Pcrit (cmH_2O)	GG Response (%max/-cmH_2O)	TP Response (%max/-cmH_2O)
#1	37	41	28 vs. 27	44 vs. 39	-7.8 vs. -9.1	1.7 vs. 1.3	-0.32 vs. -3.92	-0.76 vs. -0.59
#2	33	48	101 vs. 94	46 vs. 41	-10.1 vs. -14.2	5.1 vs. 1.2	-0.12 vs. -0.10	-0.15 vs. -0.58
#3	39	40	47 vs. 55	45 vs. 38	-8.2 vs. -10.3	N/A vs. 0.2	-0.07 vs. -0.71	-0.09 vs. -0.47
#4	25	31	10 vs. 11	20 vs. 27	-8.1 vs. -10.7	1.9 vs. 1.0	-0.02 vs. -0.13	-0.03 vs. -0.05
#5	31	47	12 vs. 18	13 vs. 12	-15.7 vs. -17.5	-4.8 vs. -0.3	-1.73 vs. -4.39	-0.84 vs. -0.26
#6	35	52	31 vs. 20	39 vs. 21	-16.9 vs. -25.1	-2.9 vs. -4.0	-1.33 vs. -0.77	-0.12 vs. -0.11
#7	35	56	45 vs. 45	52 vs. 43	-13.3 vs. -20.2	0.1 vs. 0.6	-0.07 vs. -0.02	-0.03 vs. -0.08

Values are baseline versus trazodone for each individual. Subject #1 was the female participant. AHI, apnea-hypopnea index; AI, arousal index; AT, respiratory arousal threshold; BMI, body mass index; GG, genioglossus muscle responsiveness during sleep; Max, maximum; Pcrit, critical closing pressure of the upper airway; TP, tensor palatini muscle responsiveness during sleep.

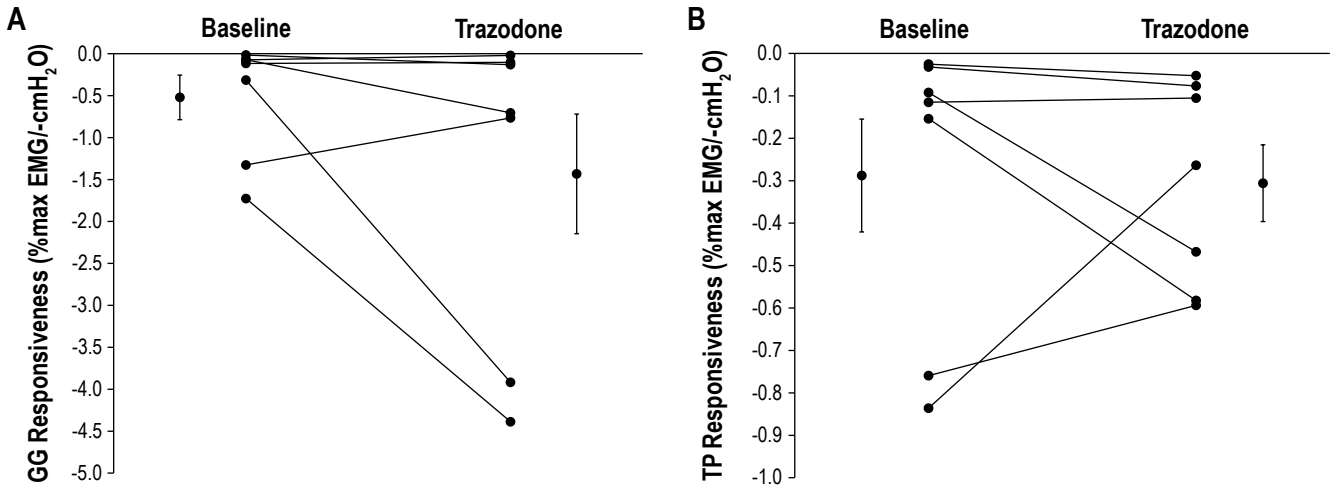

Figure 2—Slope of the relationship between **(A)** peak genioglossus (GG) and **(B)** peak tensor palatini (TP) muscle responsiveness (as a % of maximal activation) versus negative epiglottic pressure during continuous positive airway pressure reductions at baseline and following 100 mg of trazodone prior to sleep. Individual and mean ± standard error of the mean data are presented during both study nights. Note: no change in muscle responsiveness between conditions. Refer to text for further details.

Effect of Trazodone on the Respiratory Arousal Threshold

An elevated respiratory arousal threshold with trazodone is consistent with the findings of an earlier study showing that 100 mg of trazodone increases the respiratory arousal threshold by almost 50% to elevated CO_2 in nine unselected patients with OSA.[18] However, in that same study, a nonsignificant 9% increase in the arousal threshold to CPAP drops was noted during the trazodone night. Several factors may account for the apparent disparity between the current findings and those of the previous study, including patient selection and study design. First, in the prior study, on average, OSA was more severe (mean AHI 52 events/h) and arousal thresholds were also higher, varying between ~ -10 to -30 cmH_2O compared to between ~ -8 to -17 cmH_2O in the current study. Second, in the current study we focused on CPAP drops (combined mechanoreceptor and chemical stimuli). The previous study used both CPAP drops and elevated CO_2 stimuli during the same night. This combined approach resulted in approximately 50% fewer CPAP drops being delivered compared to the current study. The reduced number of replicate trials may have made it more difficult to observe a change in arousal threshold with trazodone in the prior study. Nonetheless, together these findings indicate that 100 mg of trazodone is capable of increasing the arousal threshold to respiratory stimuli in obstructive sleep apnea by 30-50%.

An increase in the arousal threshold with trazodone of this magnitude is consistent with changes in the arousal threshold observed with standard doses of other common sedatives. For example, 0.25 mg of triazolam increases the respiratory arousal threshold to airway occlusion by ~ 33% in healthy individuals[26] and by ~ 24% in patients with severe OSA.[27] Similarly, 3 mg of eszopiclone increases the arousal threshold during naturally occurring respiratory events by ~ 29% in patients with OSA who have predominantly low to moderate arousal thresholds (mean ~ -17 cmH_2O).[9]

Effects of Trazodone on Upper Airway Muscle Activity and Airway Collapsibility

Upper airway muscle activity decreases during the transition from wakefulness to sleep.[28-30] Similarly, with increasing

concentrations of propofol anesthesia, a point is reached after which there is a sudden reduction in genioglossus muscle activity and airway collapsibility increases.[31] However, when light sedation using midazolam is used to induce a sleeplike state, upper airway collapsibility is similar to natural sleep.[32] This finding is consistent with the current study in which upper airway collapsibility and sleep parameters were similar before versus after trazodone.

Whether changes in upper airway dilator muscle activity with sedatives arise due to changes in sedation depth or via a direct inhibitory effect on upper airway muscle activity is uncertain. In vagotomized, decerebrate cats the benzodiazepine diazepam preferentially reduces hypoglossal nerve activity without changing phrenic nerve activity.[33] Similar observations have been reported in lambs.[34] Conversely, in rats, other sedatives (including pentobarbital, ketamine, lorazepam, and zolpidem) may actually increase genioglossus muscle activity under certain conditions.[35-37] Phasic activity of the sternohyoid muscle during the transition from wakefulness to sleep was not impaired compared to placebo across three doses of trazodone in five English bulldogs.[17]

Few studies have examined the effects of common sedatives on upper airway muscle activity in humans. Ten mg of diazepam has been reported to reduce genioglossus muscle activity during CO_2 rebreathing in otherwise healthy older males.[38] However, this study was conducted during wakefulness and it is not clear if sleep intrusion confounded this observation. Compared with placebo, 100 mg of pentobarbital does not impair the genioglossus negative pressure reflex during wakefulness confirmed by EEG and is associated with increased phasic activity during sleep albeit with increased upper airway resistance and decreased airflow in healthy individuals.[39] Similarly, in the current study, after trazodone administration, participants tended to tolerate a greater reduction in CPAP and an approximately 50% greater reduction in ventilation and peak airflow immediately prior to arousal. These findings presumably were mediated by the increase in arousal threshold although changes were not sufficient to worsen accompanying hypoxemia.

Minute ventilation, upper airway resistance, and muscle activity on therapeutic CPAP also were not different after trazodone compared to baseline, nor was the responsiveness of the genioglossus and tensor palatini to combined mechanical and chemical stimuli over time during use of CPAP drops in the current study. These findings are consistent with data obtained in nine patients with OSA in whom minute ventilation and genioglossus muscle activity measured on therapeutic CPAP (and in response to chemical stimuli and a brief reduction in CPAP) were not different in the first half of the night compared to the second half of the night after receiving 10 mg of zopiclone.[40] Interestingly, similar to observations in the English bulldog,[17] genioglossus activity during NREM sleep remained similar to wakefulness levels on CPAP in the current study on the trazodone night. Together, these findings suggest that standard doses of zopiclone and trazodone increase the respiratory arousal threshold but do not impair upper airway muscle activity/responsiveness, airway collapsibility, or basal breathing. However, the potential for higher doses and certain classes of sedatives (e.g., benzodiazepines) to reduce upper airway muscle activity preferentially and to increase airway collapsibility remains.

Mechanistic Insight Into the Effects of Trazodone on Sleep and Breathing: Potential Interindividual Differences

The lack of a systematic change in the AHI with a standard dose of a sedative is consistent with previous studies in unselected patients.[41-47] In preselecting patients with OSA with low respiratory arousal thresholds, we anticipated that trazodone would reduce apnea severity similar to recent findings with eszopiclone whereby eight patients with OSA and a low arousal threshold had invariable reductions in their AHI.[9] There are several possibilities that may account for the apparent disparity between studies, outlined in the next paragraphs.

As stated, there are a number of possible mechanisms by which a low respiratory arousal threshold may contribute to OSA pathogenesis, including: (1) sleep fragmentation preventing deeper, more stable sleep; (2) repetitive arousals leading to respiratory control instability; and (3) inadequate respiratory stimuli to recruit pharyngeal dilator muscles. Although both sedatives increased the respiratory arousal threshold by ~ 30%, eszopiclone (a nonbenzodiazepine gamma-aminobutyric acid receptor agonist) and trazodone (a serotonin antagonist and reuptake inhibitor) are pharmacologically distinct. Accordingly, standard doses of these two agents may affect the aforementioned mechanisms and other key causes of OSA differently as will be discussed in the next paragraphs. Physiological differences between the patient groups studied also may be important.

First, although neither drug led to an increase in the proportion of N3 sleep, eszopiclone significantly decreased the proportion of lighter N1 sleep, improved sleep efficiency, and reduced the arousal index. Although similar nonsignificant reductions in N1 sleep and the arousal index were observed for trazodone in the current study, sleep efficiency did not change. Thus, trazodone may be less effective than eszopiclone in stabilizing sleep in patients with OSA who have a low arousal threshold.

Second, the effects of eszopiclone on upper airway muscle activity, airway collapsibility, and respiratory control during sleep remain unknown. However, as mentioned, similar to the current findings with trazodone, zopiclone (which is pharmacologically and functionally similar to eszopiclone) recently has been shown not to reduce genioglossus muscle activity on CPAP during sleep in OSA.[40] This observation suggests that a drug-specific effect of eszopiclone increasing genioglossus activity during sleep appears unlikely, although this possibility requires further investigation. Although trazodone did not cause major reductions in the neural output to the upper airway muscles as measured by EMG, it remains possible that, similar to recent observations with propofol anaesthesia,[48] muscle effectiveness may have been reduced, mitigating any beneficial effects of an increase in the arousal threshold on breathing stability.

Nonetheless, in the absence of marked changes in basal tone of the upper airway muscles, passive collapsibility of the upper airway also would not be expected to increase with a sedative. Indeed, this assertion is consistent with the trazodone findings in the current study. Thus, differences in induced changes in airway collapsibility between the two agents also would appear unlikely. This is important because Pcrit is an essential determinant of the importance of nonanatomical contributors to OSA.[3] Altering one non-anatomical trait such as the arousal threshold in isolation is not predicted to yield a major change in breathing stability unless Pcrit is below -2 cmH_2O.[3] In support of this

concept, six of the seven participants had Pcrit values near or above zero following trazodone, with minimal change in their AHI following trazodone. Conversely, the patient (subject #6, Table 4) who had a post-trazodone Pcrit less than -2 cmH_2O, had an approximately 35% reduction in his AHI with trazodone. Ultimately, simple, noninvasive tools to identify patients with a low arousal threshold and the other key anatomical and non-anatomical contributors to OSA will be required to translate these concepts to clinical practice.[7,49]

Another important consideration is the extent to which a sedative increases the respiratory arousal threshold beyond what is considered to be low. On average, although there were between-patient differences, arousal thresholds post-trazodone remained low (~ -15 cmH_2O). Conversely, average arousal thresholds increased to the moderate range in the prior eszopiclone study (~ -20 cmH_2O). Combining two classes of sedatives that act on different components of the arousal system in patients with OSA and a low arousal threshold may yield more pronounced changes in the respiratory arousal threshold and accompanying breathing stability, although this possibility remains untested. Interestingly, subject #6 in the current study had the biggest increase in arousal threshold with trazodone to ~ -25 cmH_2O and the largest reduction in the arousal index (~ 45%, Table 4). Had trazodone consistently led to a greater absolute shift in arousal threshold, this change may have promoted increased breathing stability, although the balance between preventing unnecessary repetitive arousals and retaining their protective role during times of need (e.g., severe hypoxemia) may begin to be comprised. Differences in plasma concentration levels of the drug also are likely to be important in determining their effects on sleep and breathing. For example, plasma concentrations following a standard dose of morphine can vary twentyfold between individuals, and this variable predicts morphine-related changes in key polysomnographic variables during sleep in OSA.[50]

Finally, the effect of trazodone and other sedatives on respiratory control, including hypercapnic and hypoxic ventilatory responses during sleep, remains untested and may differ between agents. However, basal breathing during sleep on CPAP appears to be minimally affected by zopiclone[40] or trazodone in patients with OSA. Other sedatives, including benzodiazepines, trazodone, and zolpidem, have been shown to reduce the severity of certain forms of central sleep apnea that may be due, at least in part, to a reduction in respiratory control instability (loop gain), although the precise underlying mechanisms remain uncertain.[51-55] Thus, the effects of sedatives on respiratory control are worthy of future investigation.

Methodological Considerations

Given the complexity of the measurements performed, a relatively small number of participants were tested. Thus, the sample size for the current study is insufficient to permit generalization of the findings to all patients with OSA who have a low arousal threshold. Nonetheless, the study was appropriately powered (> 80%) to detect a 3.5- cmH_2O difference with trazodone in our primary outcome measure of arousal threshold based on a sample size of seven with a between-condition standard deviation of 2.7 cmH_2O. In addition, although AHI has previously been shown to decrease in eight patients with OSA who had a low arousal threshold following administration of eszopiclone,[9] the primary goal of collecting polysomnographic data in the current protocol was to provide insight into potential changes in sleep and breathing with trazodone by linking such changes with detailed physiological parameters on an individual patient basis. Thus, determining the effects of trazodone on OSA severity *per se* may well require larger, more appropriately designed studies. Nonetheless, these data provide important mechanistic insight into the ability of a standard dose of trazodone to increase the respiratory arousal threshold and the physiological determinants that are likely to be important in mediating its effects on sleep and breathing in OSA.

Data were also acquired during NREM sleep and predominantly in men with a wide range in body weight/body mass indices. Recent studies have shown that a standard dose of zolpidem may be longer lasting and more potent in women than in men.[56] Accordingly, the effects of REM sleep, body weight/body mass index, and potential sex differences in the effects of common sedatives on sleep and breathing in OSA will be important to investigate in future studies. Finally, this was a nonrandomized physiological study and participants were not blinded to the study intervention. Thus, order and subjective influences could have biased the findings. However, study conditions were standardized between visits and sleep efficiency was similar, suggesting a lack of an order effect. Polysomnographic records also were scored blinded to the study condition and the key physiological variables were derived during sleep. Thus, subjective influences would appear highly unlikely under these conditions.

SUMMARY

The findings of this study provide novel mechanistic insight into the effects of a common sleeping agent on the propensity for respiratory arousal and its physiological effects on the upper airway and sleep disordered breathing for which data are scarce. Specifically, the findings show that 100 mg of trazodone increases the respiratory arousal threshold in patients with OSA who have a low respiratory arousal threshold without major impairment in upper airway dilator muscle activity/responsiveness, airway collapsibility, and breathing during sleep. Given the high rates of sedative use in the community, particularly in the obese, these findings are important.

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