

Trazodone Increases Arousal Threshold in Obstructive Sleep Apnea

Raphael C Heinzer^{1,2}, David P White¹, Amy S Jordan¹, Yu L Lo^{1,3}, Louise Dover¹, Karen Stevenson¹, Atul Malhotra¹

¹ Sleep Medicine Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

² Service de Pneumologie et Centre d'Investigation et de Recherche sur le Sommeil (CIRS), Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

³ Department of Thoracic Medicine, Chang Gang Memorial Hospital, Taipei, Taiwan

Correspondence and requests for reprints:

Raphael C. Heinzer, MD, MPH
Service de Pneumologie
Centre d'investigation et de recherche sur le sommeil (CIRS)
1011 CHUV Lausanne
Switzerland
Fax: +41 21 314 67 52
Email: rheinzer@post.harvard.edu

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Short Title: Effect of Trazodone on Arousal Threshold in OSA

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Abstract

A low arousal threshold is believed to predispose to breathing instability during sleep. We hypothesized that trazodone, a non-myorelaxant sleep promoting agent, would increase the effort-related arousal threshold in obstructive sleep apnea (OSA) patients.

Nine OSA patients (age 49 ± 9 yr AHI 52 ± 32 events/h) were studied on two nights, one with trazodone 100mg and one with a placebo, in a double blind randomized fashion. While on CPAP, repeated arousals were induced: 1) by increasing inspired CO_2 and 2) by stepwise decreases in CPAP level. Respiratory effort was measured with an esophageal balloon. End tidal CO_2 (EtCO_2) was monitored with a nasal catheter.

During trazodone nights compared with placebo nights, the arousals occurred at a higher EtCO_2 level (mean \pm sd): 54.9 ± 4.3 vs 49.8 ± 4.8 mmHg ($p=0.038$). When arousals were triggered by increasing inspired CO_2 level, the maximal esophageal pressure swing was greater: 19.4 ± 4.0 vs 13.1 ± 4.9 cmH₂O ($p=0.002$) and the esophageal pressure nadir before the arousals was lower: -5.1 ± 4.7 vs -0.38 ± 4.2 cmH₂O ($p=0.02$) with trazodone. When arousals were induced by stepwise CPAP drops, the maximal esophageal pressure swings before the arousals were not different.

Trazodone 100mg increases the effort-related arousal threshold in response to hypercapnia in OSA patients and allows them to tolerate higher CO_2 levels.

Word count: 200

Introduction:

Obstructive sleep apnea (OSA) syndrome is a common disorder occurring in at least 4% of middle-aged men and 2% of women [1]. It is characterized by repetitive pharyngeal collapse during sleep leading to sleep disruption, arousals and nocturnal arterial oxygen desaturation.

Apneas and hypopneas typically end with an arousal. Arousal from sleep is therefore believed to be an important mechanism for re-establishing airway patency in obstructive sleep apnea. However a recent study by Younes demonstrated that the airway opening can precede arousal and that there may be no arousal at the end of a respiratory event in some cases [2]. This finding suggests that an arousal is not always needed to restore flow after an apnea or a hypopnea. Younes also demonstrated that the occurrence of an arousal at upper airway opening (the end of the apnea) is associated with a greater ventilatory overshoot and a greater subsequent undershoot which may promote further breathing instability. This observation suggests that arousals may contribute to sleep apnea severity.

Based on this concept, some authors have tried to treat sleep apnea patients by increasing the arousal threshold with sedatives such as benzodiazepines without much success [3]. This failure may be due to a myorelaxant effect of benzodiazepine on upper airway dilator muscles. Trazodone is an antidepressant medication approved by the FDA in 1982. It appears to work by increasing brain levels of serotonin (5-HT) but is chemically unrelated to the serotonin reuptake inhibitors (SSRI's), tricyclics (TCA's) or the monoamine oxidase inhibitors (MAO inhibitors). Trazodone is also one of the most widely used sleep promoting agents in America. We hypothesized that this substance will increase the arousal threshold based on its hypnotic properties. However, unlike benzodiazepines, it should not decrease

upper airway muscle activity as serotonin (5-HT) (including specifically trazodone) has been shown to be a stimulant of upper airway muscle activity in an English Bulldog model of sleep apnea [4].

In normal subjects, arousal from NREM sleep secondary to hypoxemia without airway occlusion, whether isocapnic [5] or hypocapnic [6], is surprisingly inconsistent. Hypercapnia is generally a more potent arousal stimulus than hypoxemia [7]. Studies of hyperoxic hypercapnia have found that arousal tends to occur when the end tidal pCO₂ reaches 10-15 mmHg above the baseline waking level [8]. In sleep apnea patients the mechanisms whereby apneas lead to arousal are not completely clear. Apneas are characterized by worsening hypoxemia and hypercapnia in association with a progressive increase in respiratory effort. Although hypercapnia and hypoxemia occur during each apnea, healthy subjects usually arouse at a specific level of negative intrathoracic pressure suggesting that respiratory effort is the main stimulus to arousal [9]. However because hypercapnia without respiratory effort has been reported to induce arousals [8], an independent role of hypercapnia cannot be ruled out. We therefore sought to determine whether trazodone could increase the stimulus required to induce arousal from both increased inspired CO₂ and progressive upper airway collapse (stepwise CPAP drops). Some of the results of this study have been previously reported in an abstract.[10]

Material and methods

Study subjects:

Ten subjects with moderate to severe obstructive sleep apnea, determined by overnight polysomnography, treated with CPAP, were enrolled in the study. Subjects with any medical

problems affecting the upper airway (other than OSA), or taking any drug having an interaction with trazodone were excluded from this study. Considering the results of Gleeson et al [9] who reported that their subjects aroused at a mean oesophageal pressure of -14.7 (SD 2.4 cm H₂O), we calculated that we needed at least 7 subjects to have 80% power to detect a 4 cm H₂O (\pm SD 3 cm H₂O) difference in esophageal pressure swings (respiratory effort) between trazodone and placebo using a paired t-test with an alpha of 0.05. For the CO₂ level before arousal, we needed to study at least 6 patients to have 80% power to detect a 3 mmHg (SD 2 mmHg) difference between trazodone and placebo using a paired t-test with an alpha of 0.05.

Study design:

Subjects were studied on two nights under two different conditions, placebo or trazodone 100 mg (taken orally 90 minutes before bedtime), in a randomized (blocks of four) double blind crossover fashion. All data were analyzed before the code of the randomization was revealed. The placebo pills were produced by the hospital pharmacy and were indistinguishable from the trazodone tablets.

Methods:

For the night studies, subjects reported to the Clinical Research Center at 8:00 pm, having been without food intake for at least four hours. Paste-on electrodes were applied to the scalp, chin, chest and face to record the EEG, EMG, EOG and EKG. Nostrils were decongested (with oxymetazoline HCL) and one nostril was anesthetized with 4% lidocaine (1-1.5mls). A 10 cm deflated latex balloon linked with a pressure catheter was inserted through the decongested, anesthetized nostril and the tip of the catheter was located at the distal third of the esophagus. Once in place, the balloon was partially inflated with 0.5 ml of air and

connected to a calibrated pressure transducer. A mask was placed over the subject's nose and held in place with straps. A catheter was placed in front of the free nostril to measure end tidal CO₂ (Capnograph/Oximeter Monitor, BCI, Waukesha, WI, USA). A pulse oximeter was used to monitor blood oxygen saturation.

The subjects were allowed to fall asleep with CPAP in place at their usual level. If needed, the CPAP level was titrated to eliminate any respiratory events or flow limitation. Once stable stage 2 NREM sleep was observed, CO₂ was administered through the inspiratory line of the breathing apparatus. The CO₂ level was gradually increased until the subject aroused from sleep (Fig 1). This procedure was repeated 10 times consecutively. The maximal PEtCO₂ the subjects could tolerate before they arose as well as the esophageal pressure just before the arousal was recorded. An arousal was defined as an abrupt shift in EEG frequency which included the theta-alpha pattern and/or a frequency higher than 16 Hz (but not spindles) of 3 seconds or greater duration.

During each night study, the CPAP level was also lowered in 3 cm H₂O incremental steps. If the subject did not have an arousal for 1 minute, the next step was performed (additional 3 cm H₂O decrement in CPAP). This was continued until the subject arose from sleep (Fig 2). The nadir esophageal pressure and the maximal esophageal pressure swings just prior to arousal were recorded. This procedure was repeated 10 times.

Analysis:

Data are reported as mean \pm standard deviation (SD). All data were analyzed before the randomization code was released. The same blinded investigator scored the arousals in all the recordings. To assess the maximal respiratory effort before the arousal, both the maximal

esophageal pressure swings (mean of the last 3 inspiratory efforts before the arousals) and the esophageal pressure nadir before the arousals were determined. To compare the respiratory effort and PetCO₂ prior to arousal between placebo and trazodone, we used a paired t-test as each subject was his/her own control.

Results

Of the 10 subjects enrolled one could not complete the protocol because she felt weak and light-headed about 30 minutes after taking Trazodone 100 mg (randomization code was broken for this patient). We therefore report the results of the other nine patients.

Demographic data are reported in Table 1. During trazodone nights compared with placebo nights, the arousals occurred at a higher PEtCO₂ level (mean \pm sd): 54.9 ± 4.3 vs 49.8 ± 4.8 mmHg ($p=0.038$). When arousals were triggered by increasing inspired CO₂ level, the maximal esophageal pressure swings (mean of the last 3 inspiratory efforts before the arousals) was greater: 19.4 ± 4.0 vs 13.1 ± 4.9 cmH₂O ($p=0.002$) (Figure 3) and the esophageal pressure nadir before the arousals was lower: -5.1 ± 4.7 vs. -0.38 ± 4.2 cmH₂O ($p=0.02$) [NB patients were on CPAP]. However when arousals were induced by stepwise CPAP drops, the maximal esophageal pressure swings before arousal were not different between trazodone and placebo 16.9 ± 6.3 cm H₂O vs. 15.5 ± 6.9 ($p=0.39$) (figure 3). The difference in the esophageal pressure nadir was also not significant: -6.0 ± 8.2 vs. -5.0 ± 9.7 cm H₂O ($P= 0.53$).

Discussion:

The main finding of this study is that, in OSA patients, trazodone increases the respiratory effort related arousal threshold in response to hypercapnia and allows these individuals to tolerate a higher CO₂ level without arousal. We speculate that, in some OSA patients *without*

a highly compromised upper airway, a low arousal threshold could contribute to the severity of their disease and a medication like trazodone might reduce apnea severity. On the other hand, in patients *with* a highly compromised pharyngeal airway, airflow resistance increases markedly during sleep and complete obstruction of the upper airway is common. In these patients an increase in the arousal threshold would probably only extend the duration of the apnea as an arousal will most likely be required to re-open the collapsed upper airway.

When an individual *without* a major anatomical airway problem falls asleep, the sleep-induced fall in upper airway dilator muscles may generate only a mild increment in resistance, which will result in a hypopnea. Over time, PO_2 falls, PCO_2 rises, and ventilatory effort increases. Eventually one of two events must occur. On the one hand, the pharyngeal dilator muscles could be recruited adequately before the arousal occurs, thereby allowing sufficient ventilation such that sleep can be maintained. On the other hand, an arousal could occur, accompanied by an abrupt increase in ventilation (overshoot) which would induce a subsequent apnea or hypopnea when the individual returns to sleep. In this second situation, if an arousal occurs each time there is a mild increase in upper airway resistance, the individual will wax and wane between sleep and wake with cycling respiratory events. Depending on the prevailing mechanics of the pharyngeal airway, either central or obstructive apnea could result [11]. However, if one could increase the arousal threshold with a medication such as trazodone, the patient could potentially stay asleep long enough to recruit upper airway dilator muscles and reopen the upper airway without arousal [12]. In other words, an increase in arousal threshold in OSA patients with otherwise effective compensatory mechanisms during sleep could stabilize ventilation without arousal, at least in theory.

Other drugs have been used to treat OSA in the past. Tricyclic anti-depressant medications such as protriptyline have been shown to increase hypoglossal nerve activity in cats [13]. However this drug had only a modest effect on OSA in humans which is likely mediated through suppression of REM Sleep [14, 15]. Benzodiazepines tend to decrease hypoglossal nerve activity in cats [13] as well as the tongue muscle in humans [16] but some positive effects have been reported in humans with central sleep apnea [17]. Berry *et al.* have tried using a benzodiazepine (triazolam) to treat OSA patients. Although the authors did observe an increase in the arousal threshold, the apnea/hypopnea index did not decrease and the duration of the respiratory events mildly increased [3]. This negative result may be due to the lack of selection of OSA patients without a highly compromised upper airway. As mentioned above, to increase the arousal threshold will certainly not help OSA patients with a highly collapsible upper airway, as they likely will need an arousal to restore pharyngeal patency. Moreover benzodiazepines have a myorelaxant effect which can decrease upper airway dilator muscle activity. Trazodone, at least in theory, has the opposite effect on the upper airway musculature because of its central serotonergic effect as suggested by Veasey *et al.* [18]. Other drugs with serotonergic activity such as fluoxetine, mirtazapine and paroxetine have been tested with some success in animals, although still limited success have been reported in humans potentially due to minimal effects on the arousal threshold [15, 19-23].

There may be other reasons why suppression of arousal will not improve apnea severity. Low upper airway dilator muscles “responsiveness” to CO₂ during sleep may prevent an adequate response of pharyngeal muscles during an apnea or hypopnea, even if CO₂ levels rise substantially. Marked instability in ventilatory control (high loop gain) or high ventilatory response to arousal [24] may also contribute to OSA severity by inducing an excessive

ventilatory response to a mild respiratory disturbance and promote cyclic breathing [25]. Thus suppression of arousal with drugs such as trazodone is not likely to help all OSA patients.

As there was such a clear effect of trazodone on the CO₂ induced arousal threshold, we were surprised by the lack of a significant effect on the arousal threshold in response to a stepwise decrease in CPAP. When CPAP level was dropped, some patients may have been aroused by the facial pressure difference or startle arousals more than by the increase in upper airway resistance. Another possibility is that trazodone is affecting arousal response to chemical stimuli (i.e. CO₂) but not mechanical stimuli; however, if this were true it would challenge the notion that individuals awake at a specific esophageal pressure, regardless of the stimulus (hypoxia, loading, hypercapnia) [9].

The main limitation of this study is that we tested the effect of trazodone in artificial conditions (by increasing CO₂ and decreasing CPAP level) and not during “natural” apnea and hypopneas during sleep. We can therefore only speculate on the effect of trazodone in clinical OSA. These standardized conditions were however required to precisely compare respiratory efforts between trazodone and placebo. The hypothesis of a beneficial effect of trazodone in a subset of OSA patients with a mildly compromised upper airway and the ability to recruit muscles will thus have to be tested in future clinical trials. The best way to determine which patients may respond to an increase in arousal threshold also remains unclear at this time. Another limitation of our study is the relatively small sample size. However, we would emphasize that our sample size was determined based on rigorous power calculations as described, and that our results are quite consistent for each participant, making a spurious result unlikely.

In summary trazodone increases the respiratory effort related arousal threshold in response to hypercapnia in OSA patients and allows them to tolerate a higher CO₂ level. Arousal threshold to decrementing levels of CPAP was not altered by trazodone. The effect of trazodone on arousal threshold might open new treatment opportunities in the future for a subset of OSA patients.

Figure 1: Example of an arousal induced by an increase in CO₂ . a) general view b) 30seconds blow up of the arousal

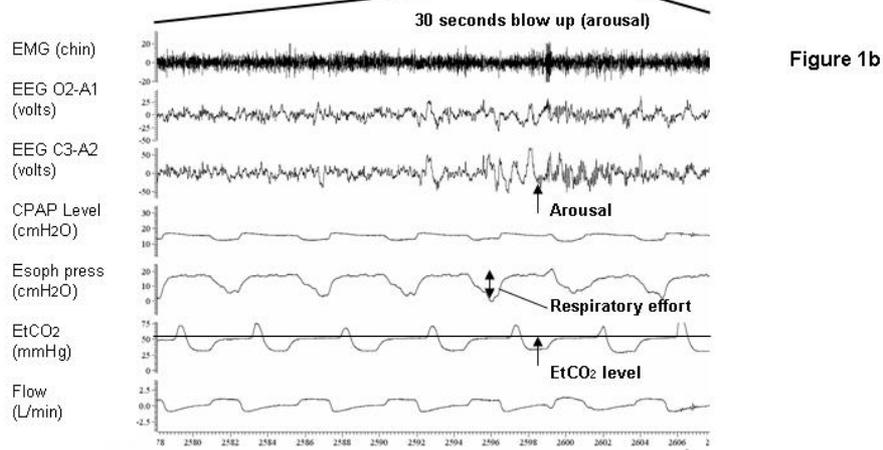
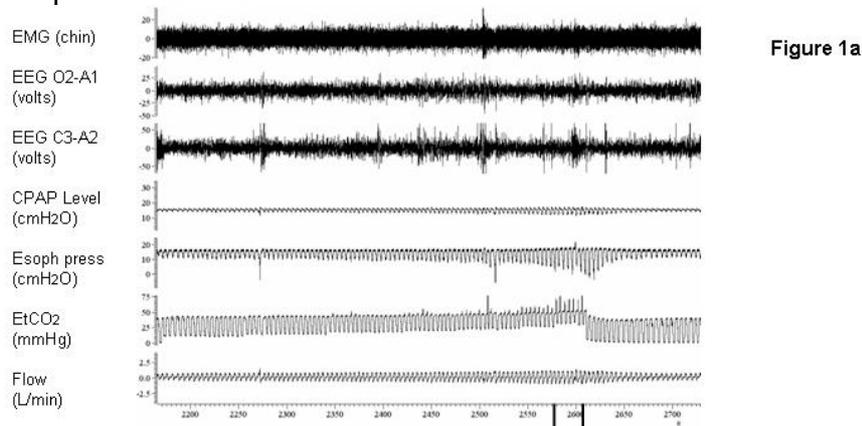


Figure 2: Stepwise CPAP level drops

Figure 2

Stepwise CPAP level Drops

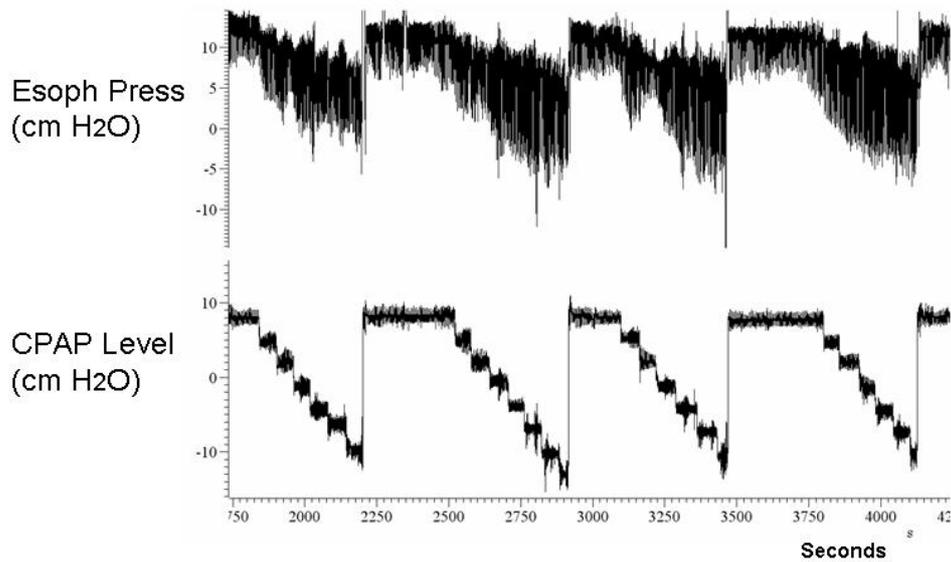


Figure 3: With trazodone, compared with placebo, subjects could tolerate higher respiratory effort before arousal only when the arousal was induced by increased EtCO₂ levels (3B) and not when it was induced by CPAP drops (3A).

Figure 3 A

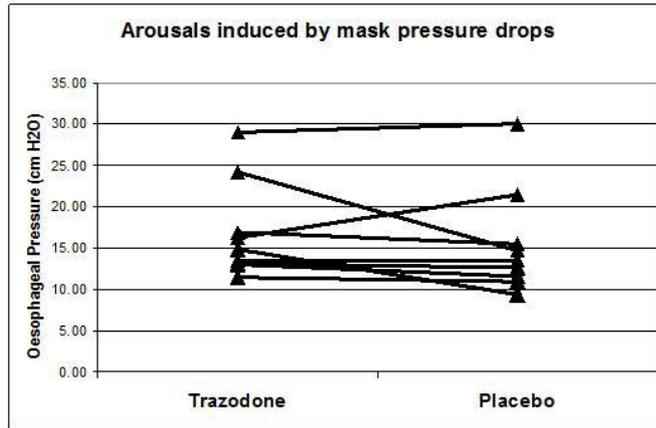


Figure 3 B

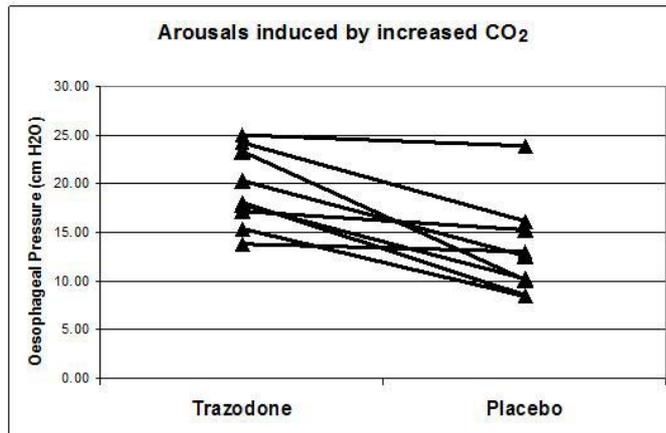


Table 1: Demographic data
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	Mean	SD	Range
Age (years)	49.9	9.5	37-64
AHI (events/h)	52	32	24-99
BMI (kg/m ²)	31.2	4.5	24.7-36.8
Male/Female	6/3		

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