

Title: Effects of Atomoxetine plus a Hypnotic on Obstructive Sleep Apnea (OSA) Severity in Patients with a Moderately Collapsible Pharyngeal Airway

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Introduction: The combination of atomoxetine and oxybutynin has some demonstrated efficacy in the treatment of OSA. Oxybutynin may play a role either as an upper airway dilator muscle activator and/or a hypnotic to improve sleep quality. As a result, we assessed the effectiveness of atomoxetine when combined with one of two hypnotics. One such drug was trazodone, a known hypnotic with additional possible effects on pharyngeal muscle activity. The other was lemborexant, an orexin antagonist. The effects of both combinations were assessed in patients with OSA and a moderately collapsible pharyngeal airway.

Methods: Recruited patients were 18-65 years of age, with an AHI4 (4% desaturation criteria) of 10-55 and a BMI of <40 kg/m². Each had to have a moderately collapsible pharyngeal airway using previously defined criteria based on the average % desaturation during obstructive events (<8%) and the ratio of hypopneas to total events (>50%). After a qualifying PSG, each patient spent 3 nights in the sleep laboratory with approximately 1 week between studies. Nights were randomized to placebo, atomoxetine 80mg plus trazodone 100mg, and atomoxetine 80mg plus lemborexant 10mg. Primary outcomes were AHI4 and the sleep apnea specific hypoxic burden (HB), the area under the SpO₂ curve associated with disordered breathing events.

Results: Fifteen patients completed the trial (median [interquartile range] age was 52 [48-55] years and BMI was 33.6 [30-35.1] kg/m². Atomoxetine + trazodone showed a strong trend for AHI4 reduction from placebo (from 18.2 [11.8-31.3] to 7.4 [5.4-16.1] events/h, p=0.064), a significant reduction in HB from placebo (from 48.2 [31.2-79.6] to 18.7 [14.9-43.5] % min/h) and a trend for a reduction in HB with atomoxetine + lemborexant (from 34.1 [12.1-128.8] to 18.7 [14.9-43.5] % min/h, p=0.055). There was no change in total sleep time or arousal index between treatment arms. Mild adverse events were reported on atomoxetine + trazodone (2/15 sinusitis, 1/15 heartburn).

Conclusion: In OSA patients with a moderately collapsible upper airway, the combination of atomoxetine plus trazodone yielded clinically meaningful improvements in measures of sleep disordered breathing and oxygenation while atomoxetine plus lemborexant produced smaller effects.

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