Editorial

# Non positive airway pressure therapies for sleep disordered breathing from the ATS 2016

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Submitted Jun 25, 2016. Accepted for publication Jul 02, 2016.
doi: 10.21037/jtd.2016.07.37
**View this article at:** http://dx.doi.org/10.21037/jtd.2016.07.37

Positive airway pressure (PAP) is the first line therapy for adult obstructive sleep apnea (OSA). However, the effectiveness of PAP is limited by treatment adherence (1). Several recent emerging therapies for OSA were presented during the Sleep and Respiratory Neurobiology sessions at the 2016 ATS meeting in San Francisco. Of particular focus was the need for appropriate patient selection and individualized therapy.

## Potential medication therapy that can increase upper airway muscle activity and treat OSA

Taranto-Montemurro *et al*. reported that desipramine, a potent norepinephrine reuptake inhibitor, reduces the state-related drop in tonic genioglossus muscle activity that occurs from wakefulness to non-REM sleep and reduces airway collapsibility in healthy controls (2). The authors then tested whether desipramine 200 mg could reduce pharyngeal collapsibility and improve sleep apnea severity in 14 OSA patients. Desipramine was found to reduce active pharyngeal critical pressure (Pcrit) (make the pharynx less collapsible when upper airway dilators are activated). But the changes in apnea hypopnea index (AHI) varied greatly across subjects. Furthermore, they found that a greater improvement was observed in patients who exhibited impaired upper airway dilator muscle effectiveness.

*Comments:* These results provide a possible rationale for new potential pharmacologic therapies for OSA. Since noradrenergic stimulation of desipramine improves AHI in a selected subgroup of patients, patient selection will be key. It would be interesting to investigate further the indications and combinations of interventions for OSA patients with impaired upper airway muscle compensation. As with other experimental pharmacologic treatments for OSA (3), more studies are needed to test if we can translate these results into clinical practice, to determine long-term safety and efficacy.

## Exercise training as an alternative treatment for OSA

Several studies have shown a favorable effect of supervised exercise training on OSA in recent years. Network meta-analysis is a meta-analysis in which multiple treatments are compared using both direct comparisons of interventions within randomized controlled trials and indirect comparisons across trials based on a common comparator. Using network meta-analysis, Iftikhar *et al*. compared the efficacy of PAP, mandibular advancement devices (MADs), dietary weight loss and exercise training in the treatment of OSA. PAP decreased the AHI most, followed by exercise training, MADs and dietary weight loss. Exercise training is the most effective in improving daytime sleepiness and sleep efficiency among all therapy.

*Comments:* Previous meta-analyses showed significant effects of aerobic or combined aerobic/resistance exercise in reducing AHI and symptoms even with minimal changes in body weight, indicating the potential value of exercise as a treatment option for OSA (4). However, the mechanisms, long-term adherence, as well as the clinical characteristics of the responders are still unclear. Further studies are needed to investigate the long-term benefits of exercise training in

reducing co-morbidities and improving outcomes in OSA patients.

## Anthropometric characteristics and phenotyping help predict the responses of MADs therapy

Edwards *et al*. investigated the effect that MADs therapy has on the key physiological traits for OSA in 14 patients (5). They found that MADs therapy reduced the AHI by improving upper-airway anatomy and collapsibility, but no changes were found in muscle function, loop gain, or arousal threshold. However, in addition to relatively high baseline passive upper airway collapsibility, a low loop gain was also predictive of better treatment outcomes.

Sutherland *et al*. set up a clinical multifactorial model for predicting the responses for MADs treatment based on testing and parameters that can be measured during the daytime. They analyzed the association of demographic, craniofacial features and anthropometric characteristics with treatment outcomes in 137 OSA patients. Responders were less obese with less severe OSA. Waist circumference and cervicomental angle were the only independent predictors that entered the final model. Those parameters correctly classified 65.7–71.8% responders and non-responders.

*Comments:* MADs have variable treatment responses in different individuals with OSA. It is important to know the effects of MADs on the phenotypic causes of OSA. These studies provide the potential methods for selecting the appropriate candidate for MADs treatment. Measuring those physiological traits in a clinical setting and adding these characteristics to the predictive models may further improve MADs efficacy (6).

## Phenotyping sleep apnea using polysomnography (PSG)

Sands *et al*. reported a new computational method to phenotype patients' upper airway collapsibility and responsiveness in OSA using clinical PSG. Collapsibility is defined as the ventilation when upper airway dilators are not activated (at eupneic respiratory drive), and the effectiveness of upper airway dilators is defined as the increase in ventilation with dilator muscle activation when ventilatory drive increases. The model was tested in 13 OSA patients with ventilation and neural ventilatory drive measurement using PAP manipulation and diaphragm EMG.

*Comments:* The efficacy of non-PAP therapy in an individual is highly dependent on subjects' baseline pathophysiological traits (6). Complicated or invasive laboratory measurements are usually needed to quantify these traits. The study enabled non-invasive assessment of pharyngeal collapsibility and muscle responsiveness from the pattern of ventilation in OSA patients. However, validation in a larger group of OSA patients will be needed. Previous publications have already discussed how to quantify arousal threshold as well as the stability of respiratory control using PSG (7,8). These methods would be helpful to select patients for individualized OSA treatment based on underlying mechanisms in a clinical setting (9).

Further research will be required to develop new therapies for sleep apnea. A personalized medicine approach is likely to emerge from an improved physiological standing of OSA pathogenesis.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* Dr. Rachel Jen, Naomi Deacon and Dr. Yanru Li have nothing to disclose. Dr. Owens has received honoraria and travel support from ResMed and Itamar Medical.

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**Cite this article as:** Li Y, Deacon N, Jen R, Owens R. Non positive airway pressure therapies for sleep disordered breathing from the ATS 2016. J Thorac Dis 2016;8(Suppl 7):S547-S549. doi: 10.21037/jtd.2016.07.37

 