Snoozeal® - Non-Invasive Intraoral Neuromuscular Stimulation Device with Clinically Proven Reduction of Primary Snoring and Mild Obstructive Sleep Apnoea

INTRODUCTION

During sleep, the upper airway dilator muscles relax causing narrowing of the pharynx and reduced airflow. In some people this results in inspiratory vibrations and audible snoring, while at the more extreme end of the spectrum the airway may repeatedly collapse during sleep, known as Obstructive Sleep Apnoea (OSA). Sleep Disordered Breathing (SDB) encompasses a spectrum of disorders from Primary Snoring (PS) to OSA characterised by the common pathophysiology process of repeated and recurrent collapse of the upper airway during sleep. These repeated airway obstructions are significant as they result in recurrent nocturnal asphyxia, fragmented sleep, major fluctuations in blood pressure, and increased sympathetic nervous system activity.[1] Furthermore, patients with untreated SDB are at increased risk of hypertension, stroke, heart failure, diabetes, depression, and car accidents.[2–9]

Although historical data traditionally states the prevalence of 4-8% of OSA in the population, literature reflects a significant increase in the prevalence over the last few decades. Recent polysomnographic data from a Swiss community sample of over 2000 individuals aged 40 to 85, indicates that 23% of women and nearly 50% of men have moderate to severe OSA, defined as >15 obstructive breathing events per hour of sleep.[10] Similarly, the estimated prevalence of moderate to severe OSA from the Wisconsin sleep cohort study in the United States has increased from 14% to 55% over the past two decades.[11] It has been calculated that nearly 1 billion adults aged 30 to 69 are estimated to have OSA globally, with the majority (60%) with mild disease (Apnoea Hypopnoea Index (AHI) ≥5 to <15 events per hour) and the remaining 40% with moderate to severe disease (AHI ≥15 events per hour).[1]

CAUSATION OF SLEEP DISORDERED BREATHING

Published literature agrees that a crowded or narrow upper airway i.e., 'impaired upper airway anatomy', is a common cause in SDB. Multiple studies using a variety of imaging techniques consistently show that, on average, the static cross-sectional area of the pharyngeal airway in people with OSA is smaller when compared to their non-OSA counterparts.[13] However, as OSA does not occur during wakefulness, OSA is clearly much more than just an anatomical problem.[14,15] Therefore, there must be other functional causes above and beyond the narrow airway that precipitates the collapse observed in these individuals. The reduction in airway muscle tone and alteration in the neural drive are considered to be the most important precipitating factors.[1,14,15]

Although there are several lifestyle practices associated with snoring and SDB (smoking, obesity, drinking, etc.), a significant proportion of individuals may snore despite not being associated with these.[14.15] The most notable change that occurs in the physiology of humans during sleep is the reduction in the tone of the muscles and increased collapsibility of the throat (pharynx) and tongue (genioglossus). Notably, there is evidence to show that the collapsibility is significantly higher in patients who obstruct (OSA) and marginally higher in patients who snore (simple snoring) when compared to individuals who do not snore (Fig 1).[16] It has been shown that when compared to "normal" individuals, the breathing passage in snorers and sleep apnoea individuals collapses at a positive rather than a negative airway pressure, thus, demonstrating a predisposition to collapse. Conversely, non-SDB predisposed individuals have an upper airway physiology that prevents collapse, such that suction intraluminal pressures of below -5cmH2O are required to close the airway. These individuals have functional physiological mechanisms that overcome the collapse of the airway associated with sleep and hence are protected from SDB.

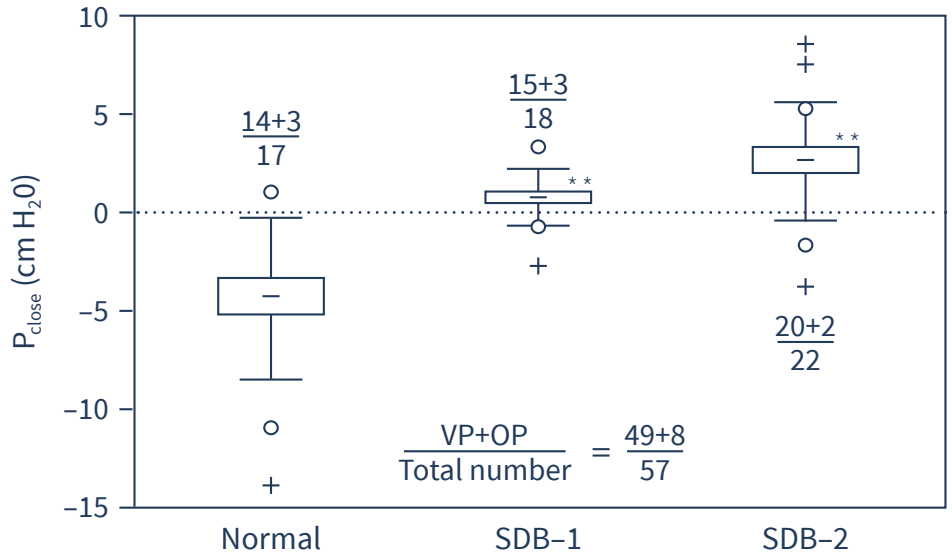


Figure 1: Critical closing pressure in healthy subjects, snorers and patients with OSA (SDB-1 = snorers, SDB-2 = Sleep Apnoea) (according to Isono et al.[16])

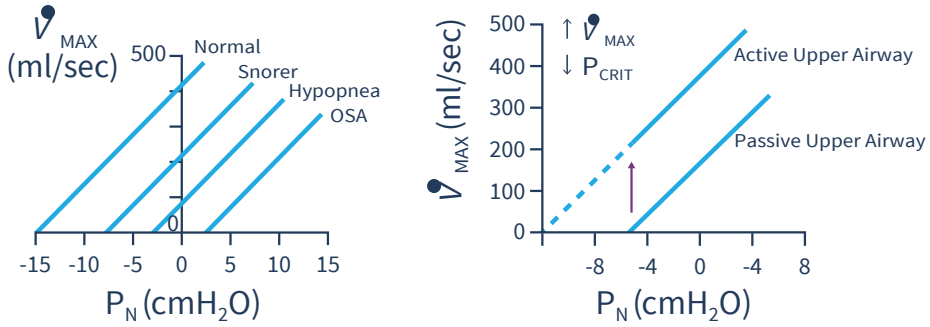
THE TONGUE AND AIRWAY COLLAPSIBILITY

The genioglossus is considered the largest muscle of the airway and the most important dilatory muscle during sleep. With sleep onset, there is a rapid reduction in pharyngeal and tongue muscle contractility.[17] Over time the respiratory stimulus (i.e., CO2 and increased pharyngeal pressure swings) and genioglossus activity progressively increase during stable non-REM sleep.[18] However, a notable proportion of individuals with OSA, fail to effectively increase genioglossus electromyography (EMG) activity or achieve inadequate tongue muscle activation to overcome the obstruction prior to arousal.[15] Thus, in SDB individuals, there is failure of the tongue muscles to generate an appropriate protective response from a neural drive or responsiveness perspective.

The reduction in tongue muscle tone has been attributed to inadequate neural signals, neurodegeneration leading to ineffective or non-responsive tongue muscle fibres, alteration in the proportion of Type 1 and 2 muscle types and ageing.[19-21] In ageing, as with other muscles, there is progressive atrophy of tongue muscle fibre structures, in particular, the dilator muscles of the upper airway which undergo transformation and degeneration.[19] There is also loss in sensory function and repeated upper airway collapse is also traumatic to upper airway mucosa, causing disturbed sensory function and inflammation.[19]

AWAKE STATE MYOFASCIAL AND NEUROMUSCULAR ELECTRICAL STIMULATION THERAPY FOR SDB

Studies show that training the upper airway muscles either by playing a wind instrument (didgeridoo)[22] or oropharyngeal exercises[23,24] can ameliorate moderate OSA. Research has demonstrated that increasing the pharyngeal muscle activity or tone, reduces the collapsibility of the airway (Fig 2).[25] A recent meta-analysis study concluded that the literature demonstrates that oropharyngeal exercises can reduce AHI by 50%.[26] The principle of training the upper airway muscles to address the airway muscle dysfunction seen in patients with OSA presents a promising and attractive alternative therapy option.



P_{CRIT} is more positive (more collapsible airway from groups of normal subjects, to snorers, and patients with hypopneas and obstructive sleep apnea (OSA).

Increases in pharyngeal muscle activity (passive to active upper airway) increase $\dot{V}_{MAX}$ and decrease P_{CRIT}, i.e., make the airway less collapsible.

Redrawn from Smith and Schwartz, Sleep Apnea: Pathogenesis, Diagnosis and Treatment, 2002

Figure 2: Upper airway collapsibility and critical closing pressure in sleeping individuals (according to Schwartz et al.[25])

There is a considerable body of literature and evidence to state that the use of transcutaneous electrical stimulation in paralyzed or inactive limbs (muscles with low or absent muscle tone) significantly improves muscle power and tone recovery.[27] Considering the muscles of the throat and tongue are of the same muscle type as of the limbs (skeletal muscle), it is logical that electrical stimulation of the pharyngeal and tongue muscles would lead to a similar effect of increased resting muscle tone and muscle tone during sleep.

The first proof of concept of daytime awake stimulation of the tongue was presented by Wiltfang in 1999.[28] He demonstrated that when compared to placebo (TENS type stimulation), daytime active stimulation of the tongue muscles for 2-weeks resulted in a significantly improved respiratory disturbance index (RDI), from 13.2 reduced to 3.9, oxygen desaturation index (from 23 to 2.8) and minimum oxygen saturation level (from 75% to 88%).

In a further study using an external daytime neck stimulator for an average of 4-weeks noted a significant drop in both AHI from 29.2 to 21.2 and in the partners witnessed snoring scale from 7.0 to 3.4 on a visual analogue scale of 1 to 10 (10 = unbearable snoring).[29]

In another study, a prospective placebo-controlled randomized study of daytime tongue stimulation vs TENS type stimulation, the number of snoring epochs decreased significantly in the active training group (baseline 63.9 ± 23.1 epochs per hour versus 47.5 ± 31.2; $P < .05$). [30] Although a significant change was noted in the objective recorded snoring, the changes in AHI were not.

These studies support the credibility that daytime or awake stage neuromuscular electrical training of the upper airway can lead to objective and clinically relevant change in sleep stage collapsibility of the airway in individuals with SDB. However, they are limited by the challenges of adequately delivering the stimulation to the genioglossus muscle and appropriate patient selection. These studies are reliant on either using submental transcutaneous electrical stimulation in isolation or combined with a single intraoral electrode on the floor of mouth. Exploratory EMG studies by the authors using these techniques identified significant variability and inadequate recruitment of the genioglossus muscle. Instead, the Snoozeal® device uses an entirely intraoral device, resting directly on the very conductive wet surface of the tongue, with a pair of electrodes above and a pair below the tongue to ensure vertical and diagonal patterns of stimulation. EMG studies (not published) using such electrode placement revealed consistent and repeatable stimulation of the genioglossus muscle using needle EMG techniques.

THE SNOOZEAL® TRANSORAL NEUROMUSCULAR THERAPY DEVICE

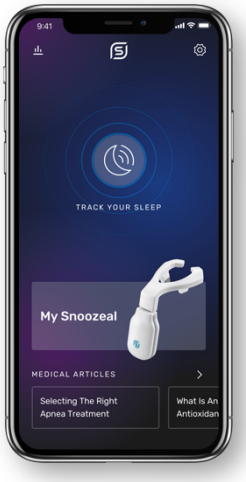
The Snoozeal® device targets the intrinsic and extrinsic pharyngeal and tongue muscles by delivering neuromuscular electrical stimulation to the back of the tongue with the purpose of increasing muscle tone and preventing excessive relaxation.

The device consists of three components:
1) Washable Flexible Electrode Mouthpiece with electrode array that fits onto the tongue.
2) Rechargeable Control Unit that attaches to the mouthpiece via a USB-C connection.
3) Remote Control Unit and/or Smartphone App that manages the functions of the device.

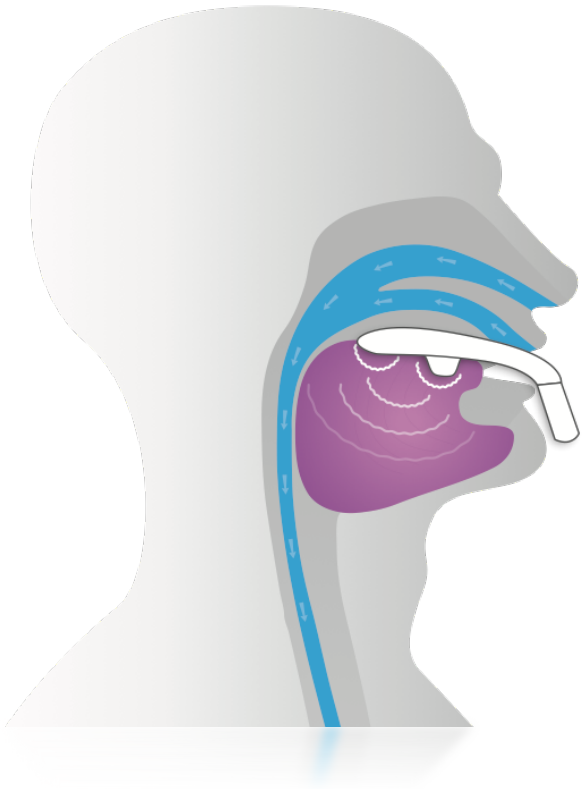
1) Mouthpiece

2) Control Unit

3a) Remote Control



3b) Snoozeal Smartphone App



The mouthpiece is placed in the mouth, with two electrodes located above and two electrodes located below the tongue. The therapy consists of a series of pulse bursts with rest periods and is used for 20 minutes during wakeful state for a period of 6-weeks. With daily use of Snoozeal®, the tongue muscle function is improved to prevent it collapsing backwards and obstructing the airway during sleep.

The Snoozeal® device has been approved for use by the EU, Australian TGA, Health Canada and awaits approval by FDA in the US.

CLINICAL TRIALS USING SNOOZEAL® DEVICE

Proof of Concept Clinical Study - Essen, Germany and Nottingham, UK

The original clinical trial with Snoozeal® was a prospective multi-centre trial of individuals with snoring and/or Mild OSA (AHI <15) (Essen, Germany and Nottingham, UK) led by Prof Boris Stuck.[31] Snoring was assessed using a bed partner reported visual analogue scale (VAS) (range 1-10,10 = unbearable snoring.) The snorers sleep quality was recorded using the Pittsburgh Sleep Quality Index (PSQI). To minimize night-to-night variation in reported VAS, recordings over a 2-week period were averaged and compared: pre-treatment (2-weeks before the start of therapy), during treatment phase (last 2-weeks of 6-week therapy period) and post-treatment (2-weeks after stopping therapy). The therapy was a 6-week daytime treatment period of intraoral tongue stimulation with the Snoozeal® device for one 20-minute treatment a day.

The study recruited a cohort of 30 of which 27 patients completed the trial (8 women and 19 men) with an average age of 44 (range 25 to 68 years). The average BMI was 29.7 (range 20.7 to 35) and AHI 9.0 (range 2.5 to 15). Eight individuals were Primary Snorers (AHI<5) and 19 had Mild OSA (AHI 5-15).

The study showed that the mean bed partner reporting snoring score reduced by 52% from 6.4 to 3.1 (p=0.001) with over 80% declaring a reduction of >40% in the reported snoring.

The change remained statistically significant for Primary Snorers (VAS reduction of 6.4 to 2.7, p=0.001) and Mild OSA patients (VAS reduction 6.6 to 3.6, p=0.001) (Fig 3).

The VAS remained stable for the 2-weeks after stopping the therapy (mean VAS 3.3) suggesting a sustained change in muscle physiology.

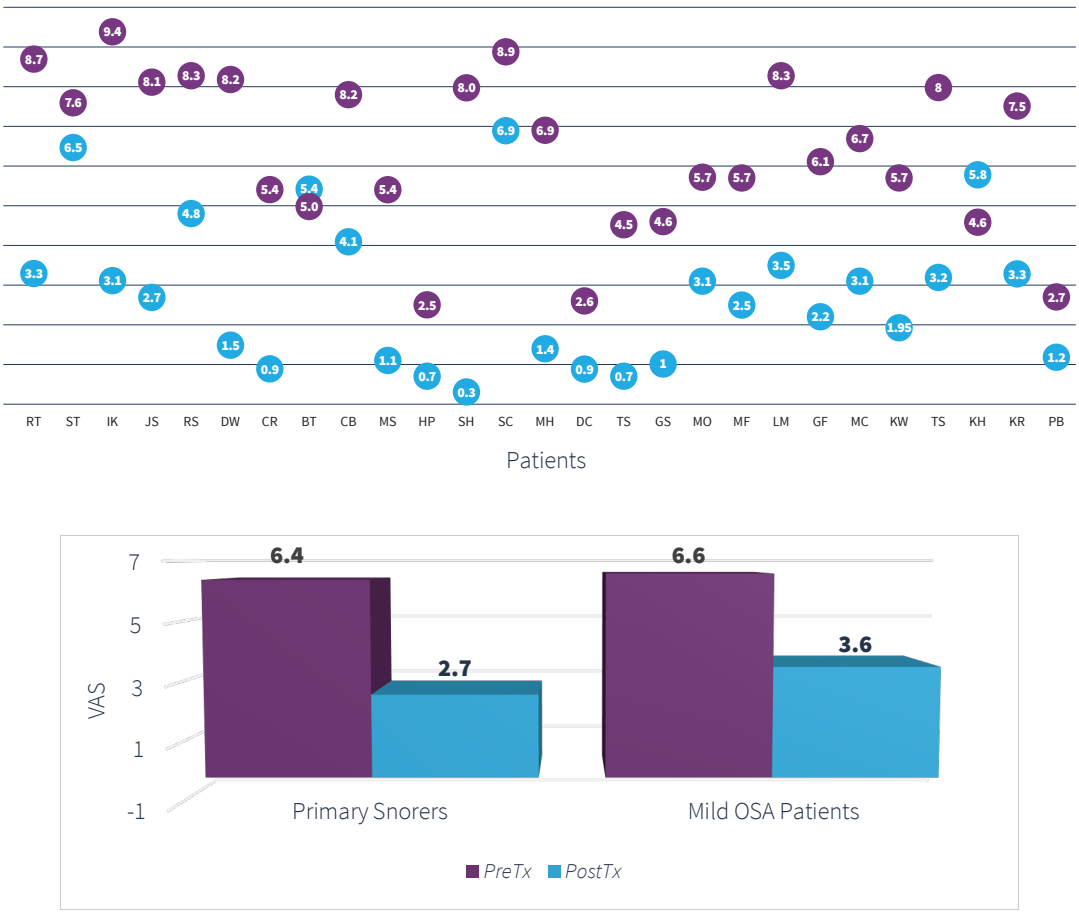


Figure 3: (a) Change in bed partner reported VAS in individual patients and (b) change in mean VAS for Primary Snoring and Mild Sleep Apnoea [31]

There was also a statistically significant improvement in 3 of 8 components of the PSQI (Sleep Quality, Sleep Disturbance and Global Score), supporting a concurrent improvement in the snorer's sleep quality with the use of the device.

Prospective Cohort Clinical Study – London, UK

This proof of concept study set up the foundation for a larger and detailed study at a London University institution led by Prof. Bhik Kotecha. (ClinicalTrials.gov identifier: NCT03829956). The aim was to use objective measures and assess the reproducibility of the outcomes of the previous study at another independent facility. This was a prospective cohort study on individuals with Primary Snoring and/or Mild OSA (AHI <15). The study assessed objective snoring (% time snoring) and respiratory parameters (AHI, RDI, Saturations) with two consecutive night sleep studies before and two consecutive night sleep studies after the use of the device. This was supplemented with bed partner VAS recordings and sleep quality questionnaires – Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). The Snoozeal® device was used for 20-minutes, once a day for a 6-week period.

Fifty patients were recruited and 46 completed the trial. One patient became pregnant during the study and 3 withdrew due to personal reasons (migration, work and personal reasons). The average age was 43 (range 26 to 70 years), with 29 men and 17 women with an average BMI of 27 (range 21 to 34). Of the 46 snorers, 24 individuals were Primary Snorers (AHI<5) and 22 had Mild OSA (AHI 5-15).

For this study population, objective snoring (% of sleep time snoring at >40dB) reduced in 98% of participants, with an average reduction of 44% while 37% of patients achieved >50% reduction in snoring time at >40dB. Loud snoring (% of sleep time snoring >50dB) reduced on average by 61%.

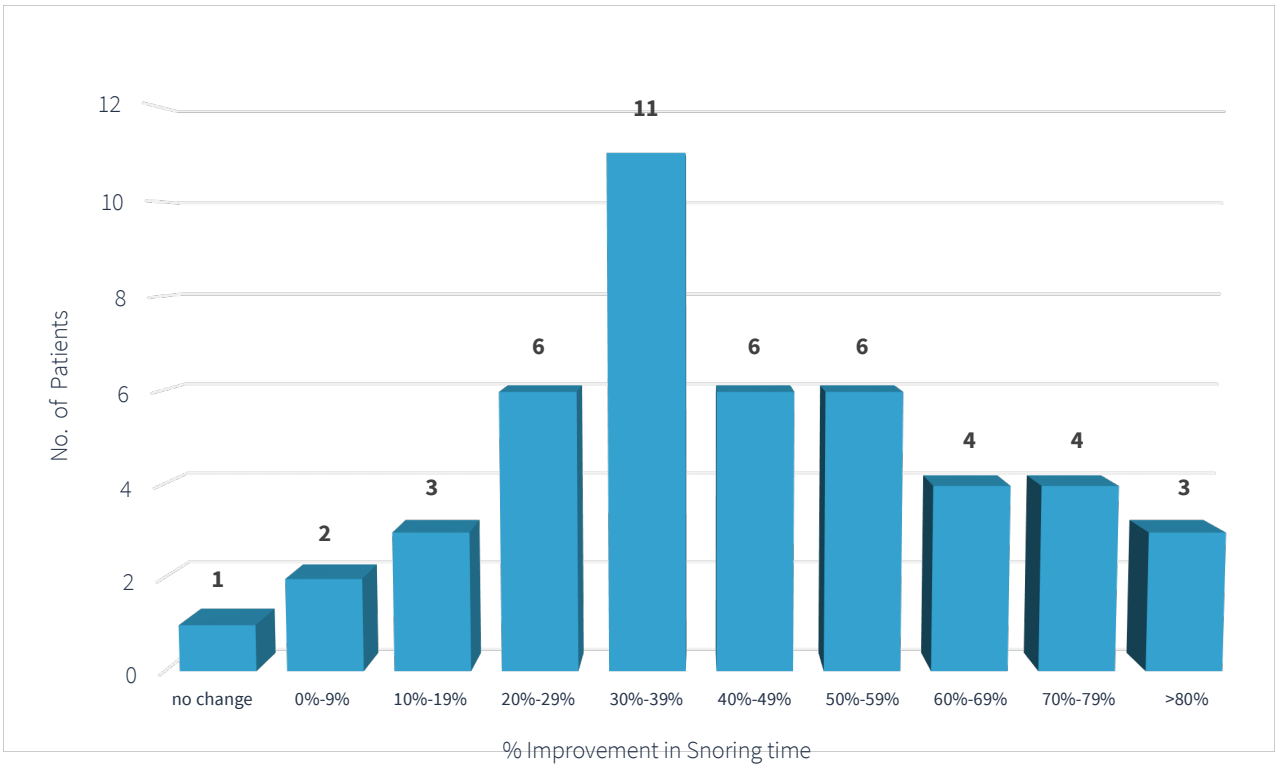


Figure 4: Reduction in Snoring Time at >40dB in patients pre- and post-therapy with Snoozeal®

Bed partner reported snoring score reduced in 82% of the patients with an average reduction of 40%, while 70% of bed partners reported an average reduction of >50% in their partners snoring.

Statistically significant improvements were identified in other objective parameters of OSA. In patients with Mild OSA (22 patients), 68% showed a reduction in their AHI with an average 47% reduction in the AHI (p=0.001) and the post-therapy average AHI almost normalised at 5.4. This was supported by a similar change in the oxygen desaturation index (ODI) with a reduction of 41% in 68% of the participants (p=0.003). Quite notably, these changes were supported by a 43% drop in ESS (p=0.001).

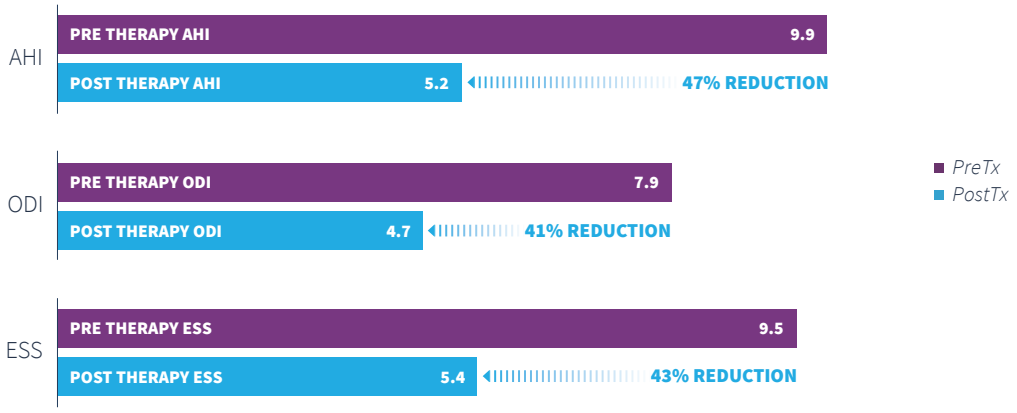


Figure 5: Average % reduction in AHI, ODI and ESS in patients with Mild OSA pre- and post- therapy with Snoozeal®

Sleep quality in these individuals improved as noted by the drop in ESS and statistically significant change in PSQI. The PSQI showed a significant change in the domain for Sleep Disturbance and Global PSQI score for the snorer and domain of day time dysfunction and Global PSQI score for the bed partner.

DISCUSSION

The strategy of one size fits all is not appropriate for a multifactorial diverse condition such as Sleep Disordered Breathing (SDB). Furthermore, although conventional therapies alleviate the obstruction when in use, they fail to modify the disease and can suffer from low compliance. Daytime neuromuscular electrical stimulation (NMES) treatment for correction of night-time airway obstruction is a novel, innovative and probably unconventional therapeutic strategy. However, the possibility of reversing the pathophysiology of SDB and not having a night-time wearable, makes this an attractive strategy to explore.

NMES involves the application of an electric current through electrodes placed over targeted muscles, to induce muscular contractions and has been shown to activate the muscle to a greater extent than voluntary muscle actions under identical conditions.[27] It has also been used to induce the activity of motor units that are difficult to activate voluntarily.[27] NMES has been shown to result in a change in myofibrillar protein expression to induce a phenotype shift of fatigue-prone to fatigue-resistant (i.e. fibre Type II to I or IIa changes) with strengthening of the cytoskeleton.[32] NMES has also been shown to result in muscle metabolic shift from glycolytic to oxidative profile, increased intracellular defence against harmful oxygen species, reverse the degenerative pre and postsynaptic tongue neural morphology associated with ageing and a shift of small to large diameter muscle fibre size with higher contractile tensions.[32,33] These established improvements mirror the anticipated causes of the neuromuscular degeneration associated with SDB as discussed before.[19-21]

Snoozeal® offers a simple and effective method of addressing the above-mentioned issues associated with Snoring and Mild OSA by reversing the causal mechanisms. Using the well-established modality of treatment of neuromuscular electrical therapy, Snoozeal® provides a targeted retraining tool to stimulate the biggest dilatory muscle of the airway- the genioglossus muscle. The clinical trial results demonstrate approximately 50% reduction in all the relevant objective measures: AHI and ODI, and efficacy in approximately 70% of individuals while objective assessment of snoring improved in practically everyone (98%). These changes are supported by corresponding improvements in sleep quality as identified by PSQI and ESS questionnaires. Furthermore, the subjective outcomes of reported snoring by bed partners, are coherent with the change seen in the objective measures. These changes in subjective outcomes have been consistent in two different populations, Germany and the UK. These studies provide strong objective and subjective evidence to support the use of Snoozeal® in the management of SDB.

CONCLUSION

Our understanding of the mechanisms of SDB is evolving. Although a narrowed upper airway is a common identifiable characteristic, increasing understanding of the neural control, airway muscle responsiveness/effectiveness and central response to increased intrathoracic pressures are changing our paradigm and management strategies for SDB and OSA. The future is likely to be more bespoke therapy(s) and move away from one size fits all. To achieve this target, we need reliable methods of assessing our patients and a larger variety of therapies that target these physiological deficiencies.

Upper airway muscle physiology forms a key cornerstone in this new paradigm. The genioglossus muscle (tongue) is the largest and most important dilatory muscle in the airway. Snoozeal® day time therapy for the tongue has proven to be effective in reducing multiple indices associated with SDB - Snoring, AHI, ODI, ESS and PSQI. Furthermore, tongue muscle training using Snoozeal® provides a “no night time wearable” option of therapy for patients and overcomes many of the risks and disadvantages associated with the currently available treatment options. Evidence suggests, Snoozeal® is a safe and effective modality of therapy for SDB.

REFERENCES

1. White DP. Sleep-related breathing disorder: 2—pathophysiology of obstructive sleep apnoea. Thorax. 1995; 50:797–804. [PubMed: 7570420]

2. Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep disordered breathing and hypertension. N Engl J Med. 2000; 342:1378–1384. [PubMed: 10805822]

3. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010;122:352–360. [PubMed: 20625114]

4. Yaggi HK, Concato J, Kernan WN, et al. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005; 353:2034–2041. [PubMed: 16282178]

5. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: The Sleep Heart Health Study. Am J Respir Crit Care Med. 2010; 182:269–277. [PubMed: 20339144]

6. Peker Y, Hedner J, Norum J, et al. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med. 2002; 166:159–165. [PubMed: 12119227]

7. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005; 365:1046–1053. [PubMed: 15781100]

8. Peppard PE, Szklo-Coxe M, Hla KM, et al. Longitudinal association of sleep-related breathing disorder and depression. Arch Intern Med. 2006; 166:1709–1715. [PubMed: 16983048]

9. Kendzerska T, Gershon AS, Hawker G, et al. Obstructive sleep apnea and incident diabetes: a historical cohort study. Am J Respir Crit Care Med. 2014; 190:218–225. [PubMed: 24897551]

10. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3:310e8.

11. Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013;177:1006e14.

12. Benjafield AV, Ayas Nt, Eastwood Pr, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019; 7: 687–98.

13. Neelapu BC, Kharbanda OP, Sardana HK, et al. Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: a systematic review and meta-analysis of cephalometric studies. Sleep Med Rev 2017;31:79e90.

14. Dempsey JA, Xie A, Patz DS, et al. Physiology in medicine: obstructive sleep apnea pathogenesis and treatment considerations beyond airway anatomy. J Appl Physiol 2014;116:3e12.

15. Eckert DJ, White DP, Jordan AS, et al. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med 2013;188:996e1004.

16. Isono S, Remmers JE, Tanaka A, et al. Anatomy of pharynx in patients with Obstructive sleep apnoea and in normal subjects. J Appl Physiology 1997;82(4):1319-1326

17. Wilkinson V, Malhotra A, Nicholas CL, et al. Discharge patterns of human genioglossus motor units during sleep onset. Sleep 2008;31:525e33.

18. Basner RC, Ringler J, Schwartzstein RM, et al. Phasic electromyographic activity of the genioglossus increases in normals during slow-wave sleep. Respir Physiol 1991;83:189e200.

19. Sériès F, Côté C, Simoneau JA, et al. Physiologic, metabolic, and muscle fiber type characteristics of musculus uvulae in sleep apnea hypopnea syndrome and in snorers. J Clin Invest 95: 20–25, 1995.

20. Sériès FJ, Simoneau SA, St. Pierre S. Characteristics of the genioglossus and musculus uvulae in sleep apnea hypopnea syndrome and in snorers. Am J Respir Crit Care Med 153: 1870–1874, 1996.

21. Saboisky JP, Butler JE, Luu BL, et al. Neurogenic changes in the upper airway of obstructive sleep apnoea. Curr Neurol Neurosci Rep 15: 12, 2015.

22. Puhan MA, Suarez A, Lo Cascio C, et al. Didgeridoo playing as alternative treatment for obstructive sleep apnoea syndrome: randomised controlled trial. BMJ. 2006; 332 (7536):266-270.

23. Guimarães KC, Drager LF, Genta PR, et al. Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome. Am J Respir Crit Care Med. 2009;179 (10):962-966.

24. Leto V, Kayamori F, Montes MI, et al. Effects of oropharyngeal exercises on snoring a randomized trial CHEST 2015; 148 (3): 683 – 691

25. Schwartz AR, Smith PL, Wise RA, et al. Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure. J Appl Physiol 1988;64:532-542

26. Camacho M, Certal V, Abdullatif J, et al. Myofunctional therapy to treat obstructive sleep apnea: a systematic review and meta-analysis. Sleep. 2015; 38 (5):669-675.

27. Sillen MJ1, Franssen FM, Gosker HR, et al. Metabolic and structural changes in lower-limb skeletal muscle following neuromuscular electrical stimulation: a systematic review. PLoS One. 2013 Sep 3;8(9):e69391

28. Wiltfang J, Klotz S, Wiltfang J, et al. First results on daytime submandibular electrostimulation of suprahyoidal muscles to prevent night-time hypopharyngeal collapse in obstructive sleep apnea syndrome. International Journal of Oral and Maxillofacial Surgery. 1999;28(1):21-5.

29. Verse T, Schwalb J, Hörmann K, et al. Submental transcutaneous electrical stimulation for obstructive sleep apnea.HNO. 2003;51(12):966-70

30. Randerath WJ, Galetke W, Domanski U, et al. Tongue-muscle training by intraoral electrical neurostimulation in patients with obstructive sleep apnea. Sleep. 2004;27(2):254-9

31. Wessolleck E, Bernd E, Dockter S, et al. Intraoral electrical muscle stimulation in the treatment of snoring. Somnologie 2018 · 22 (Suppl 2):S47–S52 https://doi.org/10.1007/s11818-018-0179-z

32. Pae EK, Hyatt JP, Wu J, et al. Short-term electrical stimulation alters tongue muscle fibre type composition. Archives of Oral Biology. 2007;52(6):544-51

33. Zaidi FN, Meadows P, Jacobowitz O, et al. Tongue anatomy and physiology, the scientific basis for a novel targeted neurostimulation system designed for the treatment of obstructive sleep apnea. Neuromodulation : Journal of the International Neuromodulation Society. 2013;16(4):376-86.

34. Ibrahim AS, Almohammed AA, Allangawi MH, et al. Predictors of obstructive sleep apnea in snorers. Ann Saudi Med. 2007;27(6):421-426.

35. Maimon N, Hanly PJ. Does snoring intensity correlate with the severity of obstructive sleep apnea? J Clin Sleep Med. 2010;6(5):475-478

36. Friberg D, Ansved T, Borg K, et al. Histological indications of a progressive snorers disease in an upper airway muscle. Am J Respir Crit Care Med. 1998;157(2):586-593.

37. Lee SA, Amis TC, Byth K, et al. Heavy snoring as a cause of carotid artery atherosclerosis. Sleep. 2008;31(9):1207-1213.

38. Calero G, Farre R, Ballester E, et al. Physiological consequences of prolonged periods of flow limitation in patients with sleep apnea hypopnea syndrome. Respir Med. 2006; 100 (5): 813 - 817.

Signifier
MEDICAL TECHNOLOGIES

Signifier Medical Technologies
The Triangle, 6th Floor
Hammersmith Grove
Hammersmith
London W6 0LG
United Kingdom

Tel: +44 (0) 2070960586
www.snoozeal.com