Signifier MEDICAL TECHNOLOGIES

eXciteOSA® - Non-Invasive Daytime Intraoral Neuromuscular Stimulation Device with Clinically Proven Reduction of Mild Obstructive Sleep Apnea and Primary Snoring

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 Apnea (OSA). Sleep Disordered Breathing (SDB) encompasses this 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 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 road traffic 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 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 (Apnea 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

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 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 apnea 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 negative intraluminal pressures 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.

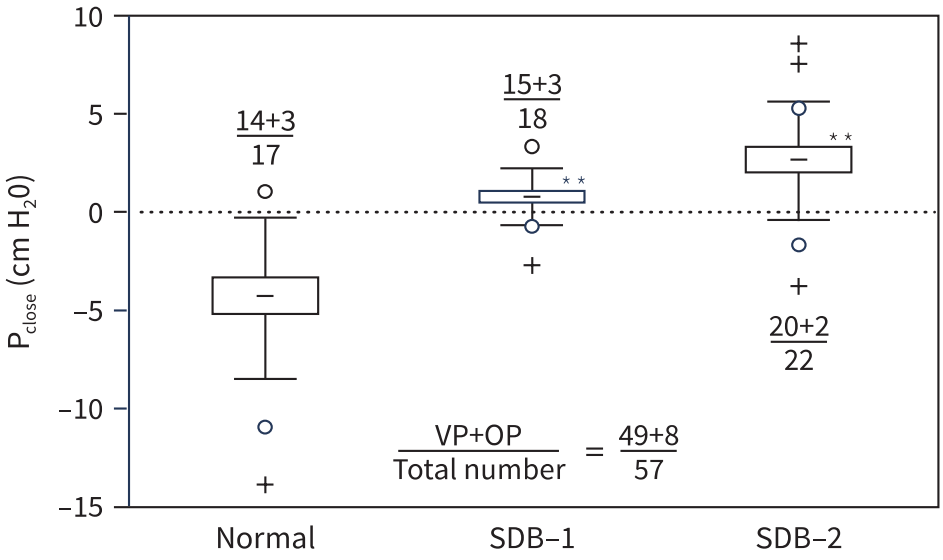


Figure 1: Critical closing pressure in healthy subjects, snorers and patients with OSA (SDB-1 = snorers, SDB-2 = Sleep Apnea) (according to Isono et al.[16])

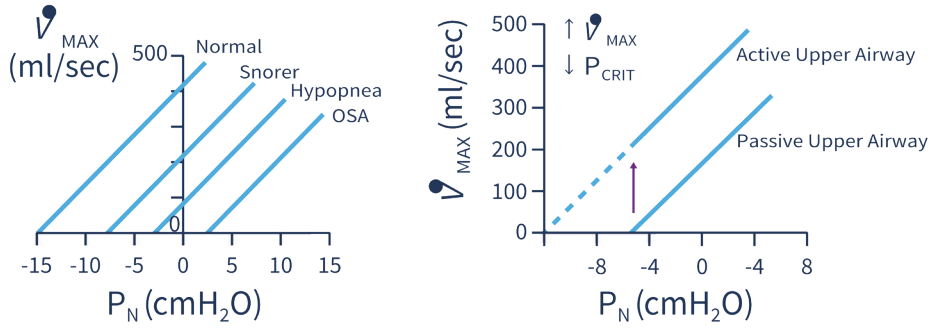
THE TONGUE AND AIRWAY COLLAPSIBILITY

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., CO_2 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 activity or achieve inadequate tongue muscle activation to overcome the obstruction prior to arousal.[15] Thus, in SDB individuals, there is a failure of the tongue muscles to generate an appropriate protective response from a neural drive or responsiveness perspective.

The reduction in tongue muscle responsiveness has been attributed to inadequate neural signals, neurodegeneration leading to ineffective or non-responsive tongue muscle fibers, alteration in the proportion of Type 1 and 2 muscle types and aging.[19-20] In aging, as with other muscles, there is progressive atrophy of tongue muscle fibers 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] A mechanistic study investigating the physiological sensorimotor functions of the upper airway during wakefulness (respiratory related evoked potentials, genioglossus and tensor palatini responses against negative pressures and tongue force and time to task failure) found that the only parameters distinguishing untreated OSA patients from healthy controls was an increased (not decreased) tongue protrusion force and reduced time to task failure (endurance).[21] They concluded that due to adaptive training effect, the tongue protrusion forces increases in OSA patients, however OSA patients are vulnerable to fatigue of upper airway dilatory muscles which contributes to disease progression.

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 concluded that the literature demonstrates that myofunctional therapy 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 dysfunctional limb muscles significantly improves muscle function 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 improved muscle functionality and responsiveness 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 analog 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-related collapsibility of the airway in individuals with SDB. However, they are limited by the challenges of adequately delivering the stimulation to the tongue (genioglossus and intrinsic muscles) 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 the mouth. Exploratory EMG studies by the authors using these techniques identified significant variability and inadequate recruitment of the genioglossus muscle. Instead, the eXciteOSA® 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 (un-published) using such electrode placement revealed consistent and repeatable stimulation of the genioglossus muscle using needle EMG techniques.

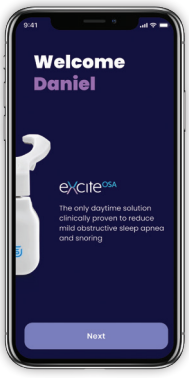
THE eXciteOSA® TRANSORAL NEUROMUSCULAR THERAPY DEVICE

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

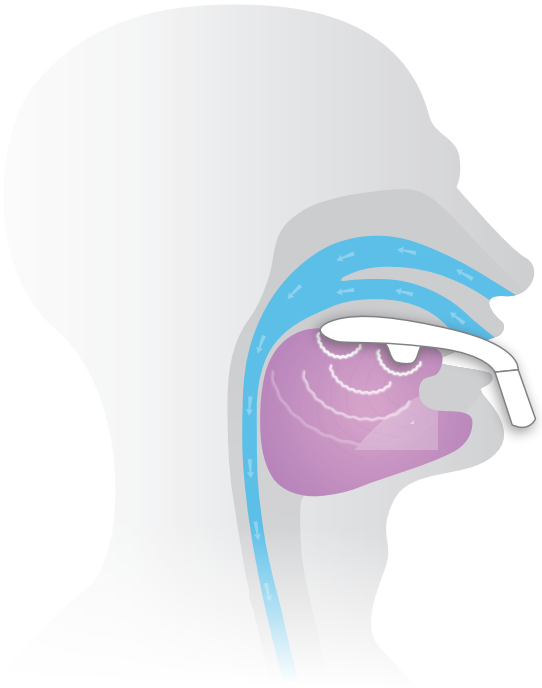
The device consists of three components:
1) Washable Flexible Electrode Mouthpiece with an electrode array that fits onto the tongue.
2) Rechargeable Control Unit that attaches to the mouthpiece via a USB-C connection.
3) Smartphone App that manages the functions of the device.

1) Mouthpiece

2) Control Unit



3) eXciteOSA® 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 the wakeful state for a period of 6-weeks. With daily use of eXciteOSA®, the tongue muscle function is improved to prevent it collapsing backwards and obstructing the airway during sleep.

The eXciteOSA® device has been approved for use by the EU, Australian TGA, Health Canada and has received FDA authorization in the US.

CLINICAL TRIALS USING eXciteOSA® DEVICE

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

The original clinical trial with eXciteOSA® was a prospective multi-center 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 analog 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 eXciteOSA® 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.

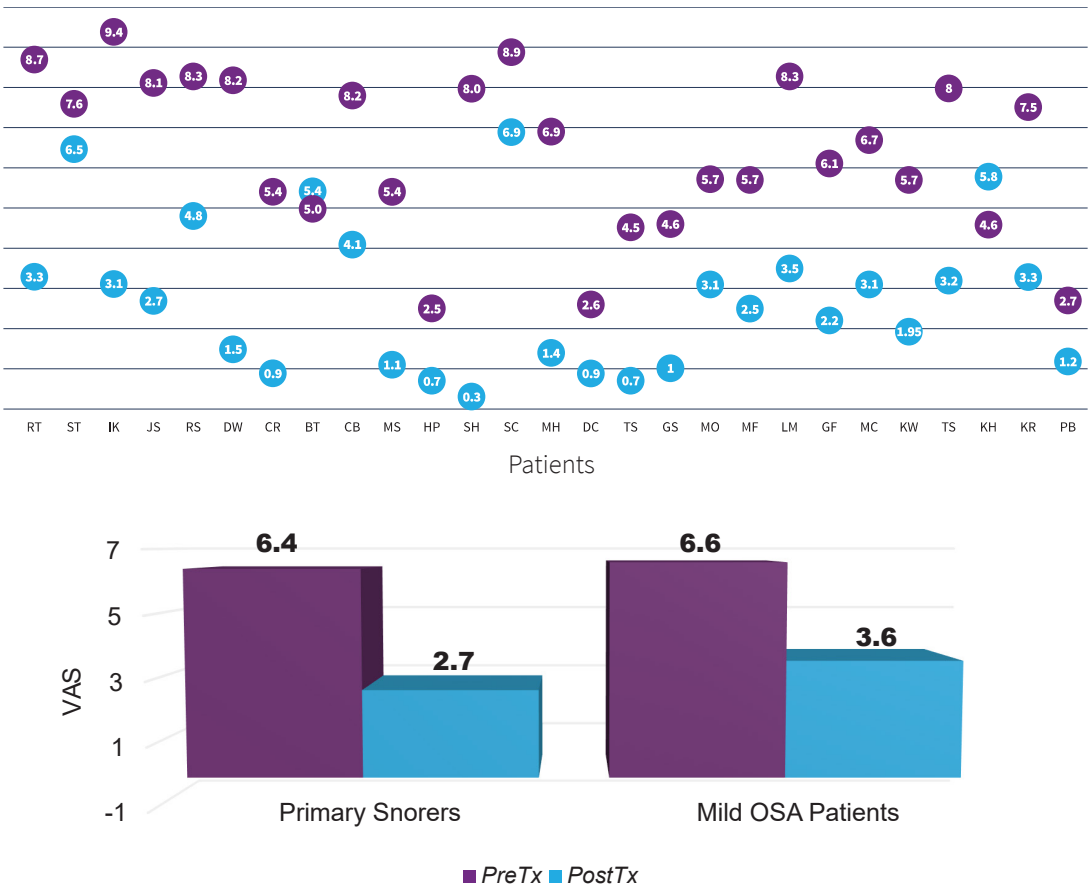


Figure 3: (a) Change in bed partner reported VAS in individual patients and (b) change in mean VAS for Mild OSA and Primary Snoring[31]

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.

Clinical Study – London, UK, Valencia, and Pamplona, Spain

A multi-centre clinical study was undertaken at a London University institution led by Prof. Bhik Kotecha. (ClinicalTrials.gov identifier: NCT03829956) along with sites at Hospital Universitario Doctor Peset, Valencia with Dr M.Carrasco, and Clínica Universidad de Navarra, Pamplona with Prof P. Baptisa.

The aim was to use validated objective measures and assess the reproducibility of the subjective outcomes of the previous study at further independent facilities. This was a prospective cohort study on individuals with Mild OSA and/or Primary Snoring (AHI <15). The study was based on Home sleep studies (WatchPAT®) to access objective snoring (% time snoring) and respiratory parameters (AHI, ODI, 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 ratings of snoring and sleep quality questionnaires – Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). The eXciteOSA® device was used for 20-minutes, once a day for a 6-week period.

125 patients were recruited and 115 completed the trial. One person was excluded from the trial following their initial oral/dental examination due to excessive dental disease needing attention. One person was unable to tolerate the device due to their gag reflex. The remaining eight potential participants withdrew for unrelated reasons. (Two became aware of their pregnancy during the pre-therapy period, a contraindication of use. Six withdrew due to changes in their personal circumstances). The average age was 46 (range 24 to 79 years), with 73 men and 42 women and an average BMI of 27 (range 20 to 34). Of the 115 snorers, 50 individuals were Primary Snorers (AHI<5) and 65 had Mild OSA (AHI 5-15).

For this study population, the mean in objective % of sleep time snoring at>40dB (i.e. all snoring sound), reduced significantly by a 41% (p<0.0001.) (Fig 4) 90% of the participants demonstrated an objective reduction in their snoring with a mean reduction of 46% in this group. Clinically significant objective changes in snoring time were also noted at snoring intensity threshold levels of 45dB (moderate snoring) and 50dB (epic snoring) with an improvement of 52% (p<0.001) and 54% (p<0.001) of the 115 patients, respectively.(Fig 4)

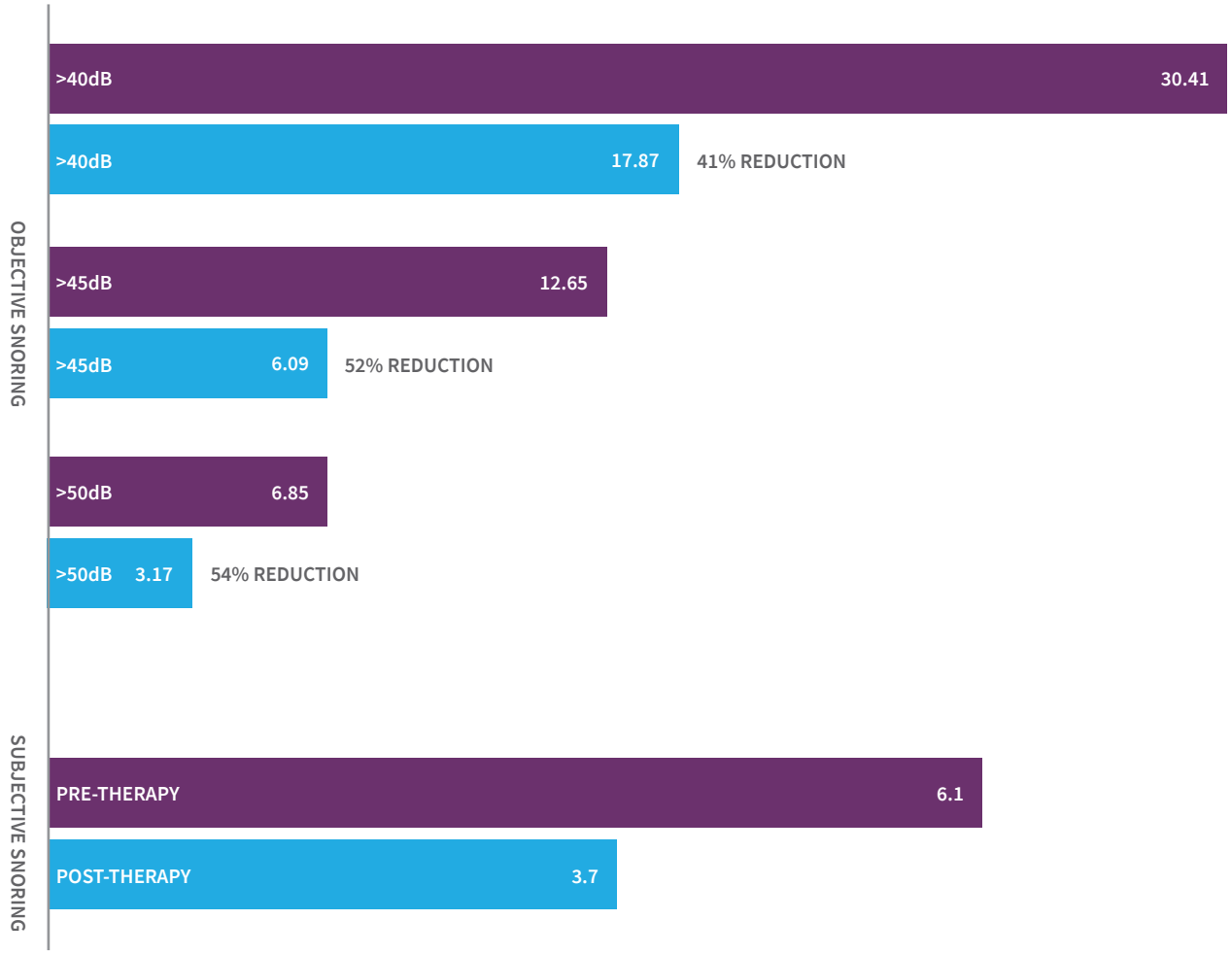


Figure 4: Average % reduction in Snoring Time and Bed partner reported snoring (VAS) in patients pre- and post- therapy with eXciteOSA®

Bed partner reported snoring (VAS) reduced significantly for the whole group from a pretherapy level of 6.1 to 3.7 (p<0.001). Some reduction in snoring was reported by 89% of the bed partners with an average reduction of 44% in this responder group.

Statistically significant improvements were identified in other objective parameters of OSA. In patients with Mild OSA (65 patients), 79% (51 patients) showed an average 52% reduction in the AHI (p<0.001), and the post-therapy AHI normalized to 4.95. In this group the oxygen desaturation index (ODI) reduced by 50% (p<0.001). These changes were supported by a notable symptomatic improvement with a 3.9 drop in ESS rating (p<0.001) and statistically significant change in PSQI (reduction from 7.17 to 5.51, p<0.001). (Fig 5).

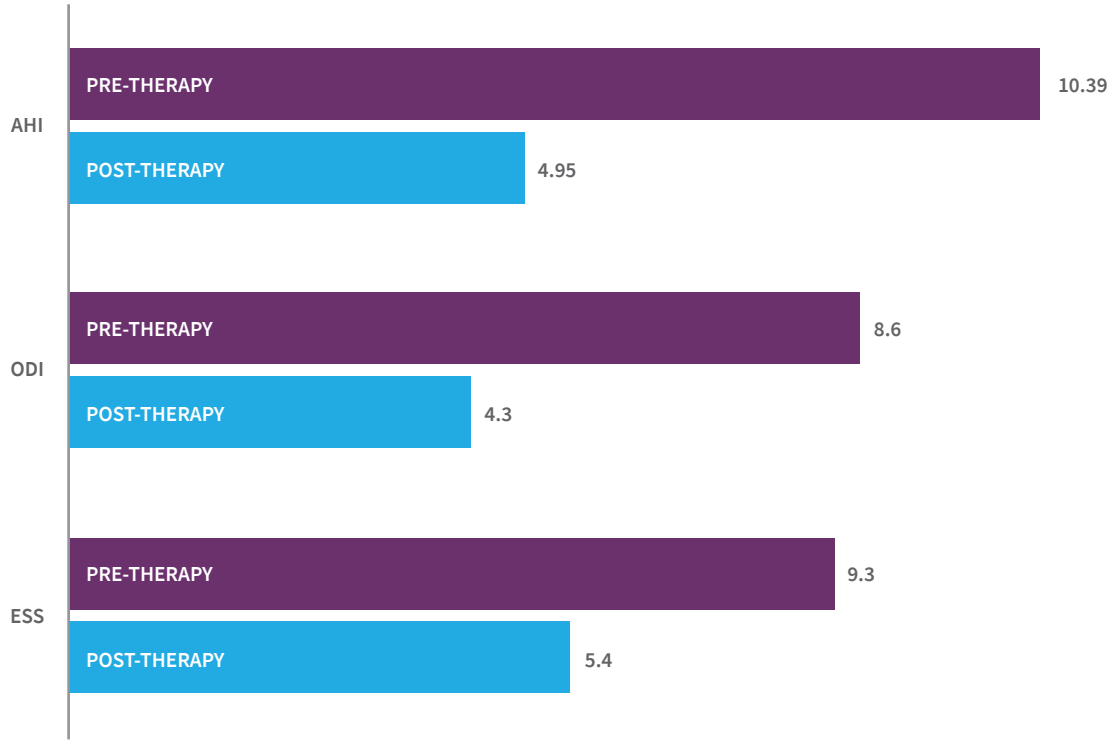


Figure 5: Average % reduction in AHI, ODI and ESS in patients with Mild OSA pre- and post-therapy with eXciteOSA® (p<0.001, for AHI, ODI and ESS)

There were no serious adverse events reported throughout the study. Side effects were reported by 17 patients (15%) with the most common being oral pooling of saliva during therapy in 12 (10.4%) patients. Additional side effects included: tongue discomfort, 10 (8.7%); tooth discomfort, 7 (6.1%); tongue tingling 7 (6.1%); filling sensitivity, 4 (3.5%); metallic taste, 3 (2.6%); gagging, 2 (1.7%) and tightness in the jaw, 1 (0.9%). All symptoms were transient and experienced only during active stimulation, with none having ongoing effects after finishing the 20 minute therapy. Furthermore, prevalence of the symptoms reduced dramatically through the therapy period, for example, 12 patients noted excessive salivation in the first week which reduced to four patients by week six.

DISCUSSION

The conventional 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) therapy 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 without the need for 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 a strengthening of the cytoskeleton.[32] NMES has also been shown to result in muscle metabolic shift from glycolytic to oxidative profile, increased intracellular defense against harmful oxygen species, reverse the degenerative pre and postsynaptic tongue neural morphology associated with ageing, and a shift to a higher contractile tensions.[32,33] These established improvements mirror the anticipated causes of the neuromuscular degeneration associated with SDB as discussed before.[19-21]

eXciteOSA® offers a simple and effective method of addressing the above-mentioned issues associated with Mild OSA and Snoring by reversing the causal mechanisms. Using the well-established modality of treatment of neuromuscular electrical therapy, eXciteOSA® provides a targeted retraining tool to stimulate the tongue (intrinsic muscles) and the biggest dilatory muscle of the airway- the genioglossus muscle. The clinical trial results demonstrate significant reductions in all the relevant objective measures: 90% of the total population saw a reduction in snoring, whilst 79% of those in the Mild OSA category saw a 50% reduction in AHI and ODI. 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, is consistent with the change seen in the objective measures. These changes in subjective outcomes have been repeatable in two different studies and studied over five different institutions and sites. These studies provide strong objective and subjective evidence to support the use of eXciteOSA® 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 tongue (intrinsic muscles) and genioglossus muscle is the largest and most important dilatory muscle in the airway. eXciteOSA® daytime 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 eXciteOSA® 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, eXciteOSA® is a safe and effective modality of therapy for SDB.

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