Interventional procedure overview of daytime intraoral neuromuscular electrical tongue stimulation using a removable device for obstructive sleep apnoea

Contents

Table 1 Abbreviations

Abbreviation	Definition
AHI	Apnoea-hypopnoea index
CI	Confidence interval
ESS	Epworth Sleepiness Score
PSQI	Pittsburgh Sleep Quality Index
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
SD	Standard deviation
VAS	Visual analogue scale

Indications and current treatment

Obstructive sleep apnoea (OSA) is a condition in which the upper airway narrows or closes during sleep when the throat muscles intermittently relax. This causes reduced breathing (hypopnoea) or breathing to temporarily stop (apnoea). OSA can lead to major neurocognitive and cardiovascular sequelae.

Management of OSA includes lifestyle changes (such as weight loss), continuous positive airway pressure, oral devices (mandibular advancement devices), neuromuscular electrical stimulation and upper airway surgery.

What the procedure involves

In this procedure, an intraoral removable device is used to deliver electrical stimulation to the intrinsic and extrinsic (genioglossus) muscles of the tongue. The aim is to improve tongue endurance and reduce airway obstruction during sleep.

A mouthpiece with an electrode array that fits onto the tongue is placed in the mouth by the patient during the daytime while they are awake. Bipolar biphasic current is then delivered for about 20 minutes with predetermined low frequency stimulation and rest periods. The mouthpiece is removed once the session is complete. The intensity of the stimulation is controlled by the patient, for example by using a smartphone app. An entire therapy usually lasts about 6 weeks, with a 20-minute daytime session each day while awake.

Outcome measures

The main outcomes include the change in the percentage of time spent snoring, respiratory parameters (AHI and ODI), sleep quality questionnaires (ESS and PSQI), and snoring intensity (VAS). Objective snoring (change in the percentage of time spent snoring) and respiratory parameters were recorded with 2 consecutive night home sleep studies before and after the procedure. A 20% reduction in snoring time was considered a clinically relevant change. In terms of sleep quality questionnaires, both patients and their bed partners completed the PSQI and ESS before, and at the end of, the therapy. The VAS was recorded daily by bed partners and its evaluation was based on the average rating over 2 weeks: pretherapy (2 weeks), end of the therapy (the last 2 weeks), and posttherapy (2 weeks). The key measures used are detailed in the following paragraphs.

The AHI is an index used to indicate the severity of sleep apnoea. It is represented by the number of apnoea and hypopnea events per hour of sleep. The AHI values for adults are categorised as:

- Normal: AHI of less than 5 events per hour
- Mild sleep apnoea: AHI of 5 or more but less than 15 events per hour

- Moderate sleep apnoea: AHI of 15 or more but less than 30 events per hour
- Severe sleep apnoea: AHI of 30 or more events per hour

The minimal clinically important difference in AHI is determined as 5 events per hour.

The ESS is a self-reported questionnaire which measures daytime sleepiness. The test includes 8 situations, with each situation being rated from 0 (no chance of dozing or sleeping) to 3 (high chance of dozing or sleeping). A total score is based on a scale of 0 to 24:

- 0 to 5 lower normal daytime sleepiness
- 6 to10 normal daytime sleepiness
- 11 to 12 mild excessive daytime symptoms
- 13 to 15 moderate excessive daytime symptoms
- 16 to 24 severe excessive daytime symptoms

The minimal clinically important improvement of the ESS lies between -2 and -3.

The ODI is a measure of insufficient blood oxygen during sleep. A normal oxygen saturation level is about 96% to 97%. When blood oxygen levels drop below 90%, ODI is considered abnormal. ODI can be used to measure the average number of desaturation episodes per hour. Desaturation episodes are generally described as a decrease in the mean oxygen saturation of 4% or more (over the last 120 seconds) that lasts for at least 10 seconds. An ODI more than 5 often predicts an AHI more than 5.

The PSQI is a self-rated questionnaire which assesses sleep quality and disturbances over a month. The measure consists of 19 individual items, creating 7 components: subjective sleep quality, sleep latency, sleep duration, habitual

sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these 7 components yields 1 global score ranging from 0 to 21, where lower scores indicate a healthier sleep quality.

The VAS is used to rank the impact of snoring by bed partners from 1 (no snoring) to 10 (intolerable snoring).

Evidence summary

Population and studies description

This interventional procedure overview is based on 128 patients with primary snoring and mild OSA from 1 single-arm clinical trial (Baptista 2021; Kotecha 2021; Nokes 2022) and 1 pilot study (Wessolleck 2018). The clinical trial by Baptista (2021) was a multicentred trial with patients recruited from the UK and Spain, and expanded the findings from Kotecha (2021) which included patients from the UK. Nokes (2022) was a secondary analysis of the subgroup of patients with mild OSA included in Baptista (2021). The pilot study by Wessolleck (2018) was a bicentric study, carried out in the UK and Germany. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 2 studies (4 papers) as the key evidence in table 2 and table 3, and lists additional relevant studies in table 5.

Of the 128 patients, 74 patients had the procedure for mild OSA. The clinical trial and the pilot study did not report the recruitment periods. Both studies had 2-week follow ups after the 6-week therapy. The mean age of patients ranged from 43 (Wessolleck 2018) to 46 years (Baptista 2021), and 66% of patients were male. The mean BMI was about 27 kg/m^2, and the mean AHI was from 6.47 (Baptista 2021) to 9.3 events per hour (Wessolleck 2018). Table 2 presents study details.

Figure 1 Flow chart of study selection

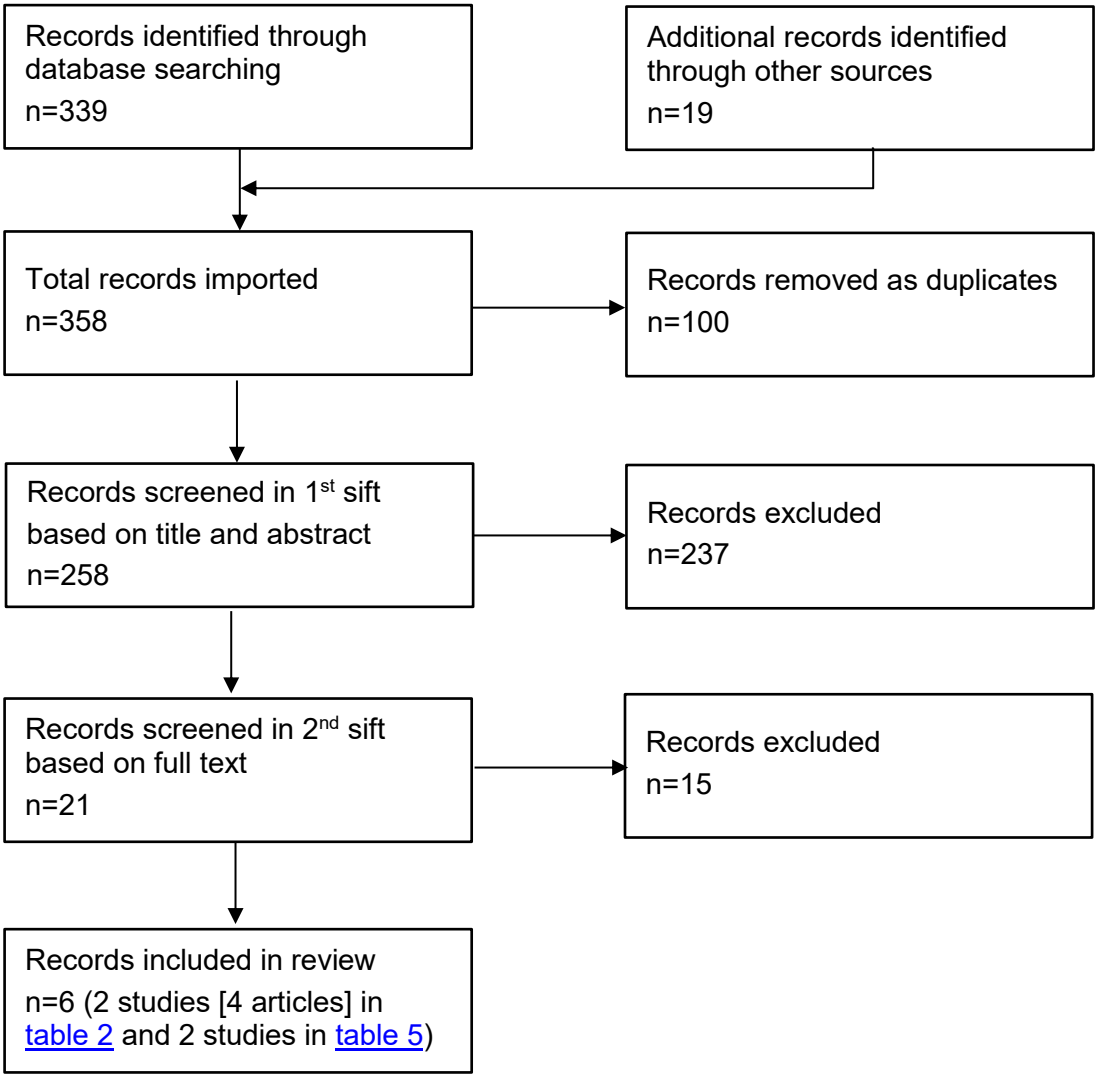

Table 2 Study details

Study no.	**First author, date** **Country**	**Patients** (male: female)	**Age** (years)	**AHI** (events per hour)	**Study design**	**Inclusion criteria**	**Intervention**	**Follow up**
1	Baptista 2021 UK and Spain	115 (73:42) (50 primary snoring; 65 mild OSA)	Mean 46	Mean 6.47	Single-arm trial (NCT03829956)	age greater than 18 years, having a live-in partner to report on snoring (VAS), and a history of more than 6 months of habitual snoring of >5 days per week, AHI <15 and BMI ≤35.	Intraoral neuromuscular electrical tongue stimulation (eXciteOSA device) for 20 minutes once daily for 6 weeks. Stimulus intensity (mean): level 5.9 at week 1 to 8.9 at week 6. Therapy adherence: 83%	2 weeks after the 6-week therapy.
	Kotecha 2021 UK	70 (44:16) (32 primary snoring; 38 mild OSA)	Mean 46	Mean 5.95	Same as Baptista (2021)	Same as Baptista (2021)	Intervention: same as Baptista (2021) Stimulus intensity (mean): leave 6 at the starting point to level 9.3 at week 6. Therapy adherence: 83.3%	Same as Baptista (2021)
	Nokes 2022 (secondary analysis of patients with mild OSA)	65 (44:21)	Median 49	Median 11.4 (range 5 to 14.9)	Same as Baptista (2021)	patients with an AHI ≥5 and <15 events per hour.	intervention: same as Baptista (2021) Therapy adherence: 85%	Same as Baptista (2021)
2	Wessolleck 2018	13 (11:2) (4 primary	Mean 43.2	Mean 9.3	Pilot study	Aged 20 to 65 years, history of more than	Intraoral neuromuscular electrical tongue	2 weeks after the

Study no.	First author, date Country	Patients (male: female)	Age (years)	AHI (events per hour)	Study design	Inclusion criteria	Intervention	Follow up
	UK and Germany	snoring; 9 mild OSA)				6 months' continuous snoring (>5 times per week), and bedpartner to document snoring intensity.	stimulation (eXciteOSA device) for 20 minutes twice daily for 6 weeks.	6-week therapy.

Table 3 Study outcomes

First author, year	Efficacy outcomes	Safety outcomes
Baptista 2021	**Mean reduction in % time snoring**: • 40 dB (all snoring): 41% (p<0.001, 95% CI 10.5 to 15.3%) • 45 dB (moderate snoring): 52% (p<0.001, 95% CI 4.74 to 8.39%) • 50 dB (epic snoring): 54% (p<0.001, 95% CI 2.30 to 5.06%) • Partners estimation: 39% reduction (p<0.001) **AHI** (mean, events per hour): pretherapy, 6.85; posttherapy, 5.03; p<0.001 **ODI 4**% (mean, events per hour): pretherapy, 5.68; posttherapy, 4.33; p<0.001 **ESS** (mean): • patients: pretherapy, 8.4; posttherapy, 5.8; mean reduction by week 6, 2.6; p<0.01; 95% CI 1.98 to 3.27 • partners: pretherapy, 6.2; posttherapy, 5.7; p=0.22 **PSQI** (mean): • patients: pretherapy, 7.16; posttherapy, 5.75; p<0.001, 95% CI 0.89 to 1.92	**Side effects**: n=17 (15%), with the most common side effect of oral pooling of saliva during utilisation (n=12, 10.4%) Additional adverse events: Tongue discomfort: n=10 (8.7%) Tooth discomfort: n=7 (6.1%) Tongue tingling: n=7 (6.1%) Filling sensitivity: n=4 (3.5%) Metallic taste: n=3 (2.6%)

First author, year	Efficacy outcomes	Safety outcomes
	• partners: pretherapy, 6.87; posttherapy, 5.94; p=0.02; 95% CI 0.15 to 1.68 **VAS** (mean): • pretherapy, 6.1; week 5/6, 3.7; p<0.001; 95% CI 2.0 to 2.69 • week 7/8, 3.8	Gagging: n=2 (1.7%) Tightness in the jaw: n=1 (0.9%)
Kotecha 2021	Proportion of patients who experienced a >25% reduction in snoring time at >40 dB: 74.3% **Mean reduction in % time snoring**: • 40 dB (all snoring): 40.84% (p<0.001, 95% CI 34.3% to 47.4%) • 45 dB (moderate snoring): 46.64% (p<0.001, 95% CI 37.60% to 55.67%) • 50 dB (epic snoring): 40.94% (p<0.001, 95% CI 30.66% to 51.23%) **AHI** (mean, events per hour): • All patients: pretherapy, 5.94; posttherapy, 5.37 • Mild OSA (n=38): pretherapy, 9.8; posttherapy, 4.7; p<0.001 **ODI** (mean, events per hour): • All patients: pretherapy, 4.92; posttherapy, 4.73 • Mild OSA (n=38): pretherapy, 7.8; posttherapy, 4.3; p<0.001 **ESS** (mean): • All patients: pretherapy, 9.0; posttherapy, 6.5; p<0.001 • Mild OSA (n=38): pretherapy, 9.0; posttherapy, 5.1; p<0.001 • Bedpartners: pretherapy, 5.8; posttherapy, 5.0; p=0.205 **PSQI** (mean): • All patients: pretherapy, 7.0; posttherapy, 5.9; p=0.004 • Bedpartners: pretherapy, 7.3; posttherapy, 6.3; p=0.029	**Side effects** (mild symptoms): n=11 Excess salivation: n=10 (14.2%) Tongue tingling/discomfort: n=7 (10%) Filling sensitivity: n=3 (4.2%) Metallic taste and gagging sensation: n=3 (4.29%) Tightness in the jaw: n=1 (4.3%)

First author, year	Efficacy outcomes	Safety outcomes
	VAS (n=61): pretherapy, 5.88; week 5/6, 3.98; p<0.001 (this benefit was sustained at week 7/8)	
Nokes 2022	**% time snoring >40 dB**: • All patients: pretherapy, 36.5%; posttherapy, 21.5%; mean reduction, 15.0±15.4% (95% CI 11.1 to 18.8%), p<0.01 • Responders (n=51): pretherapy, 37.1%; posttherapy, 20.2%; mean reduction, 16.9±16.7% (95% CI 12.2 to 21.6%), p<0.01 *Patients who experienced some reduction in their AHI were considered "responders".* • ≥50% reduction in AHI (n=28): pretherapy, 39.0%; posttherapy, 20.7%; mean reduction, 18.3±20.8% (95% CI 10.2 to 26.4%), p<0.01 **AHI** (mean[±SD], events per hour): • All patients (n=65): pretherapy, 10.2; posttherapy, 6.8; mean reduction, 3.4±5.0 (95% CI 2.2 to 4.7), p<0.01 • Responders (n=51): pretherapy, 10.4; posttherapy, 5.0; mean reduction, 5.4±2.8 (95% CI 4.7 to 6.2), p<0.01 • ≥50% reduction in AHI (n=28): pretherapy, 10.8; posttherapy, 3.5; mean reduction, 7.2±2.1 (95% CI 6.4 to 8.0), p<0.01 **ODI 4%** (mean[±SD], events per hour): • All patients: pretherapy, 8.4; posttherapy, 5.9; mean reduction, 2.5±4.6 (95% CI 1.4 to 3.6), p<0.01 • Responders (n=51): pretherapy, 8.6; posttherapy, 4.3; mean reduction, 4.3±2.7 (95% CI 3.6 to 5.1), p<0.01 • ≥50% reduction in AHI (n=28): pretherapy, 9.0; posttherapy, 3.2; mean reduction, 5.8±2.1 (95% CI 5.0 to 6.6), p<0.01 **ESS** (mean[±SD]):	Adverse events were minor, infrequent, and transient including excess drooling, tongue tingling or discomfort, tooth discomfort, and gagging (exact data was not reported).

First author, year	Efficacy outcomes	Safety outcomes
	• All patients: pretherapy, 8.7; posttherapy, 5.3; mean reduction, 3.4±4.1 (95% CI 2.4 to 4.4), p<0.01 • Responders (n=51): pretherapy, 9.3; posttherapy, 5.4; mean reduction, 3.9±3.7 (95% CI 2.8 to 4.9), p<0.01 • ≥50% reduction in AHI (n=28): pretherapy, 9.5; posttherapy, 5.2; mean reduction, 4.4±4.3 (95% CI 2.7 to 6.0), p<0.01 **PSQI** (mean[±SD]): • All patients: pretherapy, 7.3; posttherapy, 5.9; mean reduction, 1.4±2.8 (95% CI 0.7 to 2.1), p<0.01 • Responders (n=51): pretherapy, 7.2; posttherapy, 5.5; mean reduction, 1.7±2.3 (95% CI 1.0 to 2.3), p<0.01 • ≥50% reduction in AHI (n=28): pretherapy, 6.6; posttherapy, 4.8; mean reduction, 1.8±2.6 (95% CI 0.8 to 2.8), p<0.01 **VAS** (mean[±SD]): pretherapy, 6.3; posttherapy, 3.9; mean reduction, 2.4±1.8 (95% CI 1.9 to 2.9), p<0.01	
Wessolleck 2018	**VAS** (mean±SD): • All patients (n=13): pretherapy, 5.66±1.10; week 5/6, 3.16±2.58 (p<0.05 compared with pretherapy); week 7/8, 3.28±2.33 • AHI <10 (n=6): pretherapy, 5.44±1.16; week 5/6, 1.46±1.03; week 7/8, 1.66±1.11 • AHI ≥10 (n=7): pretherapy, 5.85±0.94; week 5/6, 4.61±3.16; week 7/8, 4.68±2.05	A subjective feeling of electrical stimulation in the mouth during the training phase as a short “twitching” or “tingling” (exact data was not reported).

Procedure technique

In the 2 studies, the procedure used the eXciteOSA® device (formerly known as SnooZeal©), which consists of 3 components: a control unit, a washable electrode mouthpiece, and a smartphone application. This device works by delivering bipolar biphasic current (0 to 20 Hz) through a washable flexible mouthpiece with 4 electrodes placed in pairs above and below the tongue to ensure vertical and diagonal patterns of stimulation.

Patients were instructed to use the device during wakefulness for 20 minutes once daily (Baptista 2021) or 20 minutes twice daily (Wessolleck 2018) for 6 weeks. They had full control over the intensity levels during therapy sessions and on/off functionality of the control unit and mouthpiece. They were advised to use the maximal tolerable intensity without discomfort. The clinical trial detailed stimulus intensity (from level 6 at week 1 to level 9 at week 6) and therapy adherence (83%; Baptista 2021; Kotecha 2021).

Efficacy

Change in time snoring

Change in the proportion of time snoring before and after the therapy was reported in the clinical trial. In patients with primary snoring and mild OSA, Baptista (2021) found that there were statistically significant reductions in time snoring louder than 40 dB (mean reduction, 41%), 45 dB (mean reduction, 52%) and 50 dB (mean reduction, 54%) in 115 patients recruited from the UK and Spain. Kotecha 2021 also found statistically significant reductions in time snoring at these thresholds (mean reduction of 41%, 47% and 41%, respectively) in 70 patients selected from the UK only. In patients with mild OSA (n=65), secondary analysis demonstrated a statistically significant reduction in time spent snoring louder than 40 dB, with a mean reduction of 15% (Nokes 2022).

Respiratory parameters (AHI and ODI)

Respiratory parameters were assessed before and after the therapy in the clinical trial. In patients with primary snoring and mild OSA, Baptista (2021) reported that there were statistically significant reductions after the therapy in the mean AHI and ODI based on the 4% desaturation threshold (AHI: from 6.85 to 5.03 events per hour; ODI: from 5.68 to 4.33 events per hour). However, Kotecha (2021) described that the reductions in AHI and ODI were not statistically significant (AHI, from 5.94 to 5.37 events per hour; ODI, from 4.92 to 4.73 events per hour). Secondary analysis of patients with mild OSA showed that there were statistically significant reductions in AHI (from 10.2 to 6.8 events per hour; mean reduction, 3.4 events per hour) and ODI 4% (from 8.4 to 5.9 events per hour; mean reduction, 2.5 events per hour) and that the oxygen saturation did not statistically significantly change over time (Nokes 2022).

Sleep quality (ESS and PSQI)

Sleep quality questionnaires were completed by both patients and their bedpartners before, and at the end of, the therapy in the clinical trial. The patient-reported outcomes showed a statistically significant reduction in the mean ESS in patients with primary snoring and mild OSA (mean reduction of 2.6 in Baptista 2021; mean reduction of 2.5 in Kotecha 2021), and in patients with mild OSA (mean reduction, 3.4; Nokes 2022). Based on the bedpartner-reported data, the reduction in ESS was not statistically significant (from 6.2 to 5.7 in Baptista 2021; from 5.8 to 5.0 in Kotecha 2021).

In terms of PSQI, the patient-reported data revealed that there was a statistically significant reduction in patients with primary snoring and mild OSA (from 7.16 to 5.75 in Baptista 2021; from 7.0 to 5.9 in Kotecha 2021), and in patients with mild OSA only (mean reduction, 1.4; Nokes 2022). The data reported by bedpartners

also presented a statistically significant reduction in the mean PSQI (from 6.87 to 5.94 in Baptista 2021; from 7.3 to 6.3 in Kotecha 2021).

Snoring intensity (VAS)

VAS snoring intensity was evaluated based on bedpartner's perception, and a statistically significant reduction after the therapy was found in 2 studies. In the clinical trial, Baptista (2021) reported that there was a statistically significant reduction in VAS reported by bedpartners of patients with primary snoring and mild OSA at the end of therapy, and this benefit was sustained at 2 weeks after the therapy (pretherapy, 6.1; week 5/6, 3.7; week 7/8, 3.8). Kotecha 2021 found a similar effect in VAS reduction up to 2 weeks post therapy. Secondary analysis of patients with mild OSA also showed a statistically significant reduction in bedpartner-reported VAS at the end of the therapy (mean reduction, 2.4±1.8; Nokes 2022).

In the pilot study of 13 patients with primary snoring and mild OSA, Wessolleck (2018) reported that the mean VAS statistically significantly decreased at the end of the therapy (pretherapy, 5.66±1.10; week 5/6, 3.16±2.58), and this effect remained stable up to 2 weeks after the therapy (3.28±2.33). In patients with AHI ≥10 events per hour (n=7), the mean VAS decreased from 5.85±0.94 at baseline to 4.61±3.16 at week 5/6, and 4.68±2.05 at 2 weeks after the therapy.

Safety

Baptista (2021) reported that side effects were experienced in 17 patients (15%), with the most common side effect being oral pooling of saliva during utilisation (n=12, 10%). Additional adverse events included tongue discomfort (n=10, 9%), tooth discomfort (n=7, 6%), tongue tingling (n=7, 6%), filling sensitivity (n=4, 4%), metallic taste (n=3, 3%), gagging (n=2, 2%) and tightness in the jaw (n=1, 1%). In Wessolleck (2018), patients experienced a subjective feeling of electrical

stimulation in the mouth during the training phase as a short ‘twitching’ or ‘tingling’. No serious adverse events were reported in both studies.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they have never happened (theoretical).

They listed the following anecdotal and/or theoretical adverse events: nerve injury, failure to work, and initial complications from use.

Four professional expert questionnaires for this procedure were submitted. Of the 4 professional experts, 3 experts agreed for the information they provided to be published on the website. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

Two studies (4 papers) were included in the key evidence. The clinical trial by Baptista 2021 was suitably powered, even though a potential dropout rate was not compensated. This open-label trial had a follow-up duration of 2 weeks after the 6-week therapy. The proportion of patients with primary snoring and mild OSA who did not complete the study and were excluded from the analyses was 8% (10/125) in Baptista (2021) and 19% (3/16) in Wessolleck (2018). Reasons for withdrawing varied. Both studies were sponsored by the manufacturer.

Evidence showed improvements in snoring time, respiratory parameters, sleep quality and snoring intensity, with most improvements being statistically

significant. All adverse events were minor and short lived. However, the absence of controls (sham comparator) means that the observed improvements might have been a result of a placebo effect. This possibility might be partially mitigated by the inclusion of objectively assessed endpoints. In addition, given the short follow-up duration, hard outcomes such as cardiovascular disease endpoints or neurocognitive performance were not assessed. These outcomes remain the key endpoints to consider and should be evaluated.

Further studies have been planned to include 3- and 6-month follow-up evaluations to test whether the improvements noted at 2 weeks posttherapy would sustain for a longer duration (Kotecha 2021). To date, there are 4 ongoing trials identified - 1 single-arm trial with an estimated enrolment of 200 patients and 3 trials including parallel arms:

- Efficacy of Intra-oral Neuromuscular Stimulation Training on Snoring and Mild Sleep Apnoea; (NCT04392765); Canada, Netherlands and Spain; clinical trial (open label, single group assignment); estimated enrolment, n=200; estimated study completion, September 2023.

- eXciteOSA for Treatment of Moderate Obstructive Sleep Apnea (ELMO); (NCT05252156); US; randomised controlled trial (open label); estimated enrollment, n=62; estimated study completion, December 2022.

- eXciteOSA for Treatment of Mild Obstructive Sleep Apnea (OREM); (NCT05183009); US; randomised controlled trial (open label); estimated enrollment, n=102; estimated study completion, December 2022.

- Adherence to Electrical Glossal In Situ Stimulation for Sleep Apnea (AEGIS Study); NCT04974515; US; randomised trial (open label, parallel assignment); estimated enrollment, n=40; estimated study completion, December 2022.

Despite these ongoing studies, further research is needed to include larger samples, capture long-term outcomes (1 year or longer), and conduct comparative analysis.

Related NICE guidance

Interventional procedures

- NICE interventional procedures guidance on hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea. Recommendation: special arrangements.
- NICE interventional procedures guidance on soft-palate implants for obstructive sleep apnoea. Recommendation: do not use.

Technology appraisal

- NICE technology appraisal guidance on continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome.

NICE guideline

- NICE guideline on obstructive sleep apnoea/hypopnoea syndrome and obesity hypoventilation syndrome in over 16s.

Professional societies

- British Sleep Society
- British Thoracic Society of England
- British Association of Otorhinolaryngology, Head and Neck Surgery (ENT UK)
- British Association of Oral and Maxillofacial surgery.

Evidence from patient organisations

NICE received 2 submissions from patient organisations about daytime intraoral neuromuscular electrical tongue stimulation using a removable device for obstructive sleep apnoea.

Company engagement

NICE asked the company who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

1. Baptista PM, Martinez Ruiz de Apodaca P, Carrasco M et al. (2021) Daytime neuromuscular electrical therapy of tongue muscles in improving snoring in individuals with primary snoring and mild obstructive sleep Apnea. Journal of Clinical Medicine 10(9): 1883
2. Kotecha B, Wong PY, Zhang H et al. (2021) A novel intraoral neuromuscular stimulation device for treating sleep-disordered breathing. Sleep & breathing = Schlaf & Atmung 25(4): 2083-90
3. Nokes B, Baptista PM, de Apodaca PMR et al. (2022) Transoral awake state neuromuscular electrical stimulation therapy for mild obstructive sleep apnea. Sleep and Breathing
4. Wessolleck E, Bernd E, Dockter S et al. (2018) Intraoral electrical muscle stimulation in the treatment of snoring. Somnologie 22(supplement2): 47-52

Methods

NICE identified studies and reviews relevant to daytime intraoral neuromuscular electrical tongue stimulation using a removable device for obstructive sleep apnoea from the medical literature. The following databases were searched between the date they started to 28 June 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- Patients with obstructive sleep apnoea who are 18 or older.
- Intervention or test: daytime intraoral neuromuscular electrical stimulation using a removable device.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	29/06/22	1946 to June 28, 2022
MEDLINE In-Process (Ovid)	29/06/22	1946 to June 28, 2022
MEDLINE Epubs ahead of print (Ovid)	29/06/22	June 28, 2022
EMBASE (Ovid)	29/06/22	1974 to June 28, 2022
EMBASE Conference (Ovid)	29/06/22	1974 to June 28, 2022
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	29/06/22	Issue 6 of 12, June 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	29/06/22	Issue 6 of 12, June 2022
International HTA database (INAHTA)	29/06/22	-

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1	Electric Stimulation Therapy/
2	(Elect* adj4 stimulat* adj4 therap*).tw.
3	Electrotherap*.tw.
4	or/1-3
5	(neurostimulat* or neuromuscular*).tw.
6	NMES.tw.
7	or/5-6
8	4 and 7
9	exp Sleep Apnea Syndromes/
10	Sleep apn?ea.tw.
11	Dyspnea/
12	Dyspn?ea.tw.
13	Cheyne-Stokes Respiration/
14	(Cheyne-Stokes adj4 (Respiration or breath*)).tw.
15	exp Sleep Wake Disorders/
16	(sleep* adj4 disorder*).tw.
17	Snoring/
18	snoring*.tw.
19	exp "Disorders of Excessive Somnolence"/
20	(Daytime adj4 sleepiness adj4 disorder*).tw.
21	((Somnolence* or Hypersomnolence* or Hypersomnia*) adj4 disorder*).tw.
22	or/9-21
23	8 and 22
24	((Intraoral or preamendment) adj4 (device* or daytime* or remov*)).tw.
25	22 and 24
26	8 and 24
27	eXciteOSA.tw.
28	Snoozeal.tw.
29	or/25-28
30	23 or 29
31	Animals/ not Humans
32	30 not 31

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Moffa A, Giorgi L, Carnuccio L et al. (2022) New non-invasive electrical stimulation devices for treatment of snoring and obstructive sleep apnoea: a systematic review. Sleep and Breathing	Systematic review n=4 studies	Intraoral non-invasive electrical stimulation devices can be considered a valid option to current therapies for snoring. Further studies are needed to support these interesting new devices for treatment of OSA.	Of the 4 studies, 3 relevant papers are included in the key evidence. No meta-analysis was carried out.
Nokes B, Schmickl CN, Brena R et al. (2022) The impact of daytime transoral neuromuscular stimulation on upper airway physiology – A mechanistic clinical investigation. Physiological Reports	Clinical trial n=20 patients with simple snoring and mild OSA	Transoral neurostimulation did not result in changes in genioglossal activity or upper airway collapse, but other beneficial effects were noted suggesting a need for additional mechanistic investigation.	This was a mechanistic clinical investigation, assessing the physiological effects of transoral neurostimulation on genioglossus activity and markers of inspiratory flow limitation. Also, the number of patients with mild OSA was unclear and the relevant outcomes were not reported separately.