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Electrical stimulation as a therapeutic approach in obstructive sleep apnea — a meta-analysis

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Abstract

Purpose Electrical stimulation of the upper airway dilator muscles is an emerging treatment for obstructive sleep apnea (OSA). Invasive hypoglossal nerve stimulation (HNS) has been accepted as treatment alternative to continuous positive airway pressure (CPAP) for selected patients, while transcutaneous electrical stimulation (TES) of the upper airway is being investigated as non-invasive alternative.

Methods A meta-analysis (CRD42017074674) on the effects of both HNS and TES on the apnea-hypopnea index (AHI) and the Epworth Sleepiness Scale (ESS) in OSA was conducted including published evidence up to May 2018. Random-effects models were used. Heterogeneity and between-study variance were assessed by I^2 and τ^2, respectively.

Results Of 41 identified clinical trials, 20 interventional trials ($n = 895$) could be pooled in a meta-analysis (15 HNS [$n = 808$], 5 TES [$n = 87$]). Middle-aged (mean ± SD 56.9 ± 5.5 years) and overweight (body mass index 29.1 ± 1.5 kg/m^2) patients with severe OSA (AHI 37.5 ± 7.0/h) were followed-up for 6.9 ± 4.0 months (HNS) and 0.2 ± 0.4 months (TES), respectively. The AHI improved by − 24.9 h^{-1} [95%CI − 28.5, − 21.2] in HNS (χ^2 79%, I^2 82%) and by − 16.5 h^{-1} [95%CI − 25.1, − 7.8] in TES (χ^2 7%, I^2 43%; both $p < 0.001$). The ESS was reduced by − 5.0 (95%CI − 5.9, − 4.1) ($p < 0.001$).

Conclusion Both invasive and transcutaneous electrical stimulation reduce OSA severity by a clinically relevant margin. HNS results in a clinically relevant improvement of symptoms. While HNS represents an invasive treatment for selected patients with moderate to severe OSA, TES should be further investigated as potential non-invasive approach for OSA.

Keywords Obstructive sleep apnea · Hypoglossal nerve stimulation · Transcutaneous electrical stimulation · Upper airway collapse

Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder affecting 14% of adult men and 5% of adult women [1], and prevalence is rising with obesity. Patients with OSA have recurrent complete or partial collapse of the upper airway during sleep resulting in apneas and hypopneas. Physiological and epidemiological observational studies have suggested an independent association between moderate-to-severe OSA and adverse cardiovascular outcome [2]. Furthermore, symptomatic OSA may lead to road traffic accidents, and a diminished health-related quality of life [3, 4]. Therefore, offering a treatment to these patients is important. Continuous positive airway pressure (CPAP) is the standard treatment for OSA as it abolishes apneas and hypopneas effectively [5–7]. However, it has been reported that up to 50–60% of patients may be non-adherent to the long-term use of CPAP [1, 8, 9]. Alternative treatments are required to increase treatment adherence. Mandibular advancement devices (MADs) are recommended as an alternative to CPAP, but their use is primarily for patients who have mild-to-moderate OSA and a predisposing upper airway anatomy or symptomatic

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patients who are unable to tolerate CPAP [10, 11]. CPAP is more effective than MADs in reducing polysomnographic indices of OSA severity, like the apnea-hypopnea index (AHI) and the oxygen desaturation index (ODI), but they are comparable in improving daytime sleepiness and quality of life [12, 13].

Electrical stimulation of the upper airway dilators is an emerging treatment for OSA. Electrical current can be delivered invasively via hypoglossal nerve stimulation (HNS) or, non-invasively, via transcutaneous electrical stimulation (TES) of the upper airway muscles. HNS involves implanting an electrical stimulation device unilaterally under general anesthesia, with a sensing lead to inspiratory intercostal muscles and a stimulating lead to the hypoglossal nerve. Drug-induced sleep endoscopy (DISE) is used to select patients based on the upper airway collapse pattern. In contrast, TES is a completely non-invasive approach applying transcutaneous electrical stimulation in the submental area using transcutaneous electrical stimulation devices, attached to skin patches bilaterally.

HNS has obtained healthcare approval (e.g., FDA, NICE) for patients with moderate to severe OSA [14] although the evidence on the effectiveness and long-term effects of HNS is limited [15, 16]. TES is not yet implemented into clinical practice but proof-of-concept studies have shown promising results. TES requires low currents to avoid discomfort on the skin and awakening, and it is therefore more likely to be a therapeutic option in less severe OSA. However, trials with an adequate follow-up time and a large enough sample size demonstrating effectiveness and feasibility of TES are currently missing.

The aim of this meta-analysis was to assess the effectiveness of both invasive and non-invasive upper airway electrical stimulation on objective measures of OSA severity (AHI, ODI) and subjective daytime sleepiness.

Methods

Trial registration and reporting

The systematic review and meta-analysis was registered on PROSPERO (2017:CRD42017074674), and the results are reported according to the PRISMA statement [17].

Search strategy and study selection

Medline/PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to identify clinical trials on electrical stimulation of the upper airway in human patients with OSA, up to May 2018. In addition, reference lists of identified studies and clinical trial registers were screened. The following search terms were used: (electrical stim* OR hypoglossal nerve stim* OR upper airway stim*) AND (OSA OR sleep apn* OR sleep-disorder*). No language restriction was applied. The literature search was independently performed by three authors (CR, AG, EIS).

Eligibility

In order to be eligible, trials must have studied the effect of either nocturnal invasive hypoglossal nerve stimulation or non-invasive stimulation of upper airway muscles for a minimum of one night in adult patients with OSA, defined by an apnea-hypopnea index (AHI) of at least 5 events/h. Trials studying patients with other sleep-related breathing disorders than OSA were excluded. Randomized controlled trials (RCTs) as well as other controlled or uncontrolled interventional trials were considered. Trials must have reported at least the AHI as a measure of OSA severity at baseline and at follow-up together with a variability measure or the within- or between-group difference along with the 95% confidence interval in an uncontrolled or a controlled trial, respectively. Sub-studies or follow-up studies including at least in part the same patient cohort as the original study were excluded.

Outcomes

The primary outcome was the effect of electrical stimulation on OSA severity reported by the AHI. Secondary outcomes were the effect of electrical stimulation on the 4%-ODI, the Epworth Sleepiness Scale (ESS) as measure of subjective sleepiness, the association between the effect of electrical stimulation on AHI and pre-specified baseline characteristics (AHI at baseline, body mass index (BMI), length of follow-up, sample size), and the comparison between invasive and non-invasive electrical stimulation in terms of effectiveness in reducing AHI. The role of drug-induced sleep endoscopy for patient selection on the effectiveness of HNS in reduction of AHI was an explorative outcome.

Data extraction

Data extraction was independently performed by three authors (EIS, AG, CR), and discrepancies were resolved through group discussion.

Quality assessment and risk of bias assessment

The Robins-I tool for assessing the risk of bias in non-randomized interventional studies has been used and adapted as there is no ideal tool for single arm trials [18]. The tool was developed by the Cochrane Bias Methods Group. The risk of bias is categorized based on the highest risk in several domains (e.g., confounders, outcome assessment, missing data). Two reviewers (CR, AG) independently assessed the risk of

bias of included trials using the ROBINS-I tool [18]. Agreement on discrepancies was found by group discussion.

Statistical methods

Data are either presented as mean (standard deviation) if normally distributed or median (interquartile range) if non-normally distributed. Mean (standard deviation or standard error) of outcomes for each arm at each visit was used to estimate within- and between-group changes for those studies not reporting these. If outcome data from several visits were reported, data from the latest follow-up visit were used. The standard error of the change in response to the intervention was calculated, as previously reported [19]. Heterogeneity was assessed using the χ^2 and the I^2 statistic. Between-study variance was tested using τ^2 statistics.

Random-effects pairwise meta-analyses were conducted to assess the effect of electrical stimulation on each outcome. Mann-Whitney *U* tests or ANOVA were used to compare studies using HNS and TES. Forest plots were used to summarize the pooled effects. A funnel plot and Egger's test were used to assess publication bias and small study effects. Random-effects meta-regressions (unadjusted, without covariates) were used to assess the effect of trial characteristics on the effect of electrical stimulation on the AHI.

Results

Search results and included studies

Of 41 identified clinical trials, 13 sub- or follow-up-studies were excluded. Four studies not reporting the primary outcome AHI [20–23], one study [24] applying TES only during daytime wakefulness and not during sleep, and three studies [25–27] not reporting outcome data in sufficient detail had to be excluded. Finally, data of 20 studies (N = included = 946, n = analyzed = 895) were pooled in a meta-analysis with the primary outcome of AHI [15, 28–46]. This included 15 HNS trials (N = 859, n = 808) and five TES trials (N = 87, n = 87) (Fig. 1). Only one trial reporting on TES was a randomized controlled trial [15].

Study characteristics

Middle-aged (age 56.9 ± 5.5 years) and overweight (BMI 29.1 ± 1.5 kg/m^2) patients with moderate to severe OSA (AHI 37.5 ± 7.1 h^{-1}) were included and followed-up for 5.2 ± 4.6 months (Table 1). There was no significant difference in age, BMI, or OSA severity between patients in the HNS and the TES trials. However, follow-up in HNS studies was significantly longer (6.9 ± 4.0 months) than in TES studies (0.2 ± 0.4 months) (p = 0.002) (Table 2).

Effect of electrical stimulation on primary outcome

Overall, there was a decrease of the AHI by 23.5 h^{-1} (95%CI − 20.0, − 27.0) in response to electrical stimulation (p < 0.001, χ^2 96.7, I^2 80.3%). This reduction corresponds to a reduction in the AHI of 63% compared to baseline (residual AHI 14.0 h^{-1}). A reduction in the AHI was found for both HNS (AHI − 24.9 [95%CI − 28.5, − 21.2] h^{-1}, χ^2 78.8, I^2 82.2%, p < 0.001) (Fig. 2) and TES (AHI − 16.5 [− 25.1, − 7.8] h^{-1}, χ^2 7.04, I^2 43.2%, p < 0.001) (Fig. 3), corresponding to a reduction in the AHI by 66% for HNS (residual AHI 13.1 h^{-1}) and by 46% for TES (residual AHI 18.0 h^{-1}) compared to baseline. There was no statistically significant difference in the change in the AHI between HNS and TES studies (p = 0.13; Table 3).

Effect of electrical stimulation on ODI and ESS

Overall, in the 8 studies that reported on changes in ODI in response to electrical stimulation, there was a reduction of − 11.6 h^{-1} (95%CI − 8.0, − 15.1; p < 0.001), corresponding to a decrease in the ODI by 44% compared to baseline. In these studies, the ODI was reduced to a slightly lower extent than the AHI (reduction of 44% in ODI vs 49% in AHI). Across the 11 studies that reported a change in the ESS (all HNS studies), ESS was reduced by 5.0 (95%CI 4.1, 5.9; p < 0.001; Table 3) points.

Meta-regression analyses

There was no evidence of a statistically significant association between the effect of electrical stimulation on AHI and baseline AHI, BMI, age, or sample size (Fig. 4).

DISE vs non-DISE

There was no statistically significant difference (p = 0.56 in a non-parametric comparison test) in reduction of AHI by HNS in studies using DISE for patient selection (AHI − 23.7 h^{-1} [95%CI − 21.8, −36.3]; p < 0.001) compared to those not using DISE (AHI − 20.4 h^{-1} [95%CI − 14.9, −25.8]; p < 0.001; Table 3).

Risk of bias

The funnel plot (Fig. 5) and the Egger's test (p = 0.65) did not indicate any relevant small study effect. The risk of bias for non-randomized studies was assessed using the ROBINS-I tool [18]. Those 19/20 interventional trials that were uncontrolled interventional trials were already at moderate risk of bias due to the lack of a control group. Using the ROBINS-1-tool for non-randomized interventional trials categorizing the risk of bias based on the highest risk of several domains, 6

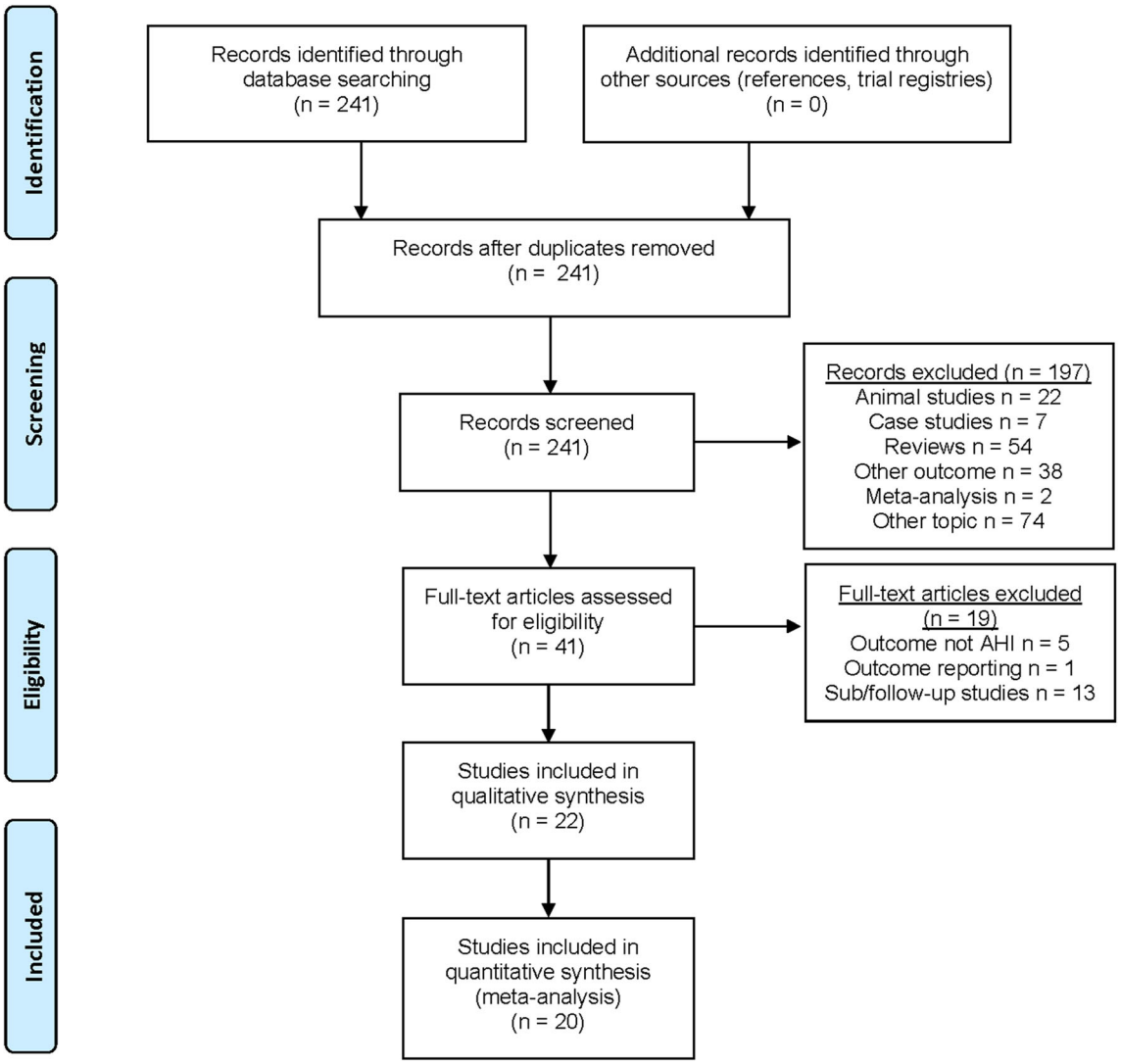

Fig 1 PRISMA flow chart

studies showed a moderate risk of bias (lack of control group) and 13 studies showed a serious risk of bias (mainly due to patient selection or study design of a retrospective cohort analysis). In summary, the risk assessment showed a high risk of bias for the primary outcome of AHI in most of the studies with a favorable outcome towards the intervention (Table 4).

Discussion

This is the first meta-analysis investigating the treatment effect of both methods of electrical upper airway stimulation—invasive HNS and non-invasive TES of the upper airway—on objective and subjective outcomes in OSA. HNS and TES were both found to significantly reduce AHI in OSA by a clinically relevant amount of 66% and 46%, respectively. Both techniques did not abolish OSA completely but improved OSA severity to a lower category, which implies a relevant risk reduction in terms of symptoms and vascular outcomes. HNS has been shown to result in a relevant reduction in daytime sleepiness. The effect of TES on subjective sleepiness has not been assessed yet due to limited follow-up periods. Based on the current findings and in view of the invasive approach of HNS and the lower currencies in TES for comfort reasons, HNS is a potential invasive treatment alternative to CPAP for moderate to severe OSA in selected patients and TES potentially offers a non-invasive alternative for less severe OSA if proven feasible as long-term treatment.

Despite approval of HNS as treatment for OSA, the evidence for this method is not based on randomized controlled trials. HNS is an invasive approach with surgery under general anesthesia and therefore the evidence for its use should be carefully reviewed, as evidence from clinical registries becomes available. Although the non-invasive method of TES has been shown to be effective in proof-of-concept trials, it is a less targeted approach where responder and patient selection

Table 1 Baseline characteristics

	Study	Stimulation type	Follow-up	Sample size analyzed	DISE selection	Age (years)	BMI (kg/m^2)	AHI (h^{-1})	ODI (h^{-1})
1	Parikh, 2018	HNS	12 months	14	0	70.2 (5)	28.3 (2.0)	38.4 (10.6)	–
2	Schwab, 2018	HNS	12 months	13	0	53.0 (9.2)	27.8 (1.6)	33.5 (10.4)	–
3	Boon, 2018	HNS	4 months	293	0	59.2 (11.2)	29.2 (3.8)	35.6 (15.3)	–
4	Shah, 2018	HNS	2.5 months	17	1	62.4 (8.9)	28.0 (2.0)	38.9 (12.5)	–
5	Mahmoud, 2017	HNS	2 months	47	1	61.0 (1.8)	29.2 (0.8)	39.3 (2.8)	–
6	Huntley, 2017	HNS	2 months	97	1	61.9 (11.0)	28.5 (3.8)	35.6 (18.3)	–
7	Steffen, 2018	HNS	12 months	56	1	56.8 (9.1)	28.8 (3.6)	31.2 (13.2)	28.5 (16.6)
8	Friedman, 2016	HNS	6 months	43	0	54.9 (11.1)	30.8 (3.7)	34.9 (22.5)	32.4 (22.3)
9	Pengo, 2016[a]	TES	1 night	36	0	50.8 (11.2)	31.1 (5.2)	34.4 (23.6)	36.8 (24.4)
10	Kent, 2016	HNS	3 months	20	1	64.8 (12.0)	26.5 (4.2)	33.3 (13.0)	–
11	Strollo, 2014	HNS	12 months	124	1	54.5 (10.2)	28.4 (2.6)	32.0 (11.8)	28.9 (12.0)
12	Kezirian, 2014	HNS	12 months	31	1	52.4 (9.1)	32.4 (3.6)	45.4 (17.5)	20.9 (17.3)
13	Vanderveken, 2013	HNS	6 months	16	1	55.0 (11.0)	28 (2.0)	38.5 (11.8)	–
14	Van de Heyning, 2012	HNS	6 months	8	1	53.6 (11.9)	28.9 (2.1)	38.9 (9.8)	32.1 (15.1)
15	Eastwood, 2011	HNS	6 months	19	0	53.6 (9.2)	32.7 (3.6)	43.1 (17.4)	16.8 (4.4)
16	Hu, 2008	TES	Split-night	22	0			30.9 (21.5)	33 (25.1)
17	Verse, 2003	TES	1 month	15	0	59.6 (10.7)	29.3 (3.6)	29.2 (12.5)	21.1 (13.1)
18	Schwartz, 2001	HNS	6 months	8	0	49.9 (8.1)	28.4 (4.5)	52.4 (20.4)	–
10	Hida, 1993/94	TES	5 nights	8	0	51.4 (3.2)	28.1 (1.3)	53.8	–
20	Miki, 1988	TES	1 night	6	0	–	–	–	–

HNS studies that reported on invasive hypoglossal nerve stimulation, *TES* studies that reported on transcutaneous electrical stimulation, *DISE* studies which included drug-induced sleep endoscopy as part of patient selection, *BMI* body mass index, *AHI* apnea-hypopnea index, *ODI* oxygen desaturation index

[a] Mean (SD) data for BMI, AHI and ODI for Pengo et al. [15] provided by authors from raw data, as only median (IQR) presented in manuscript

criteria have not yet been identified clearly. New treatment concepts are required to allow a more individualized treatment approach to the phenotypically diverse patient group with symptomatic OSA. Therefore, different methods might be

Table 2 Baseline characteristics by group

	All ($n = 895$)	HNS ($n = 808$)	TNS ($n = 87$)	p value ANOVA
Age (years)	56.9 (1.3)	57.5 (1.4)	53.9 (2.8)	0.312
BMI (kg/m^2)	29.1 (0.4)	29.1 (0.4)	29.0 (0.5)	0.979
AHI (h^{-1})	37.5 (1.6)	38.0 (1.4)	35.5 (6.1)	0.538
Follow-up (months)	5.2 (1.0)	6.9 (1.0)	0.2 (0.2)	0.002

Baseline characteristics (mean (SE)) compared between studies using invasive hypoglossal nerve stimulation (HNS) and transcutaneous electrical stimulation (TES)

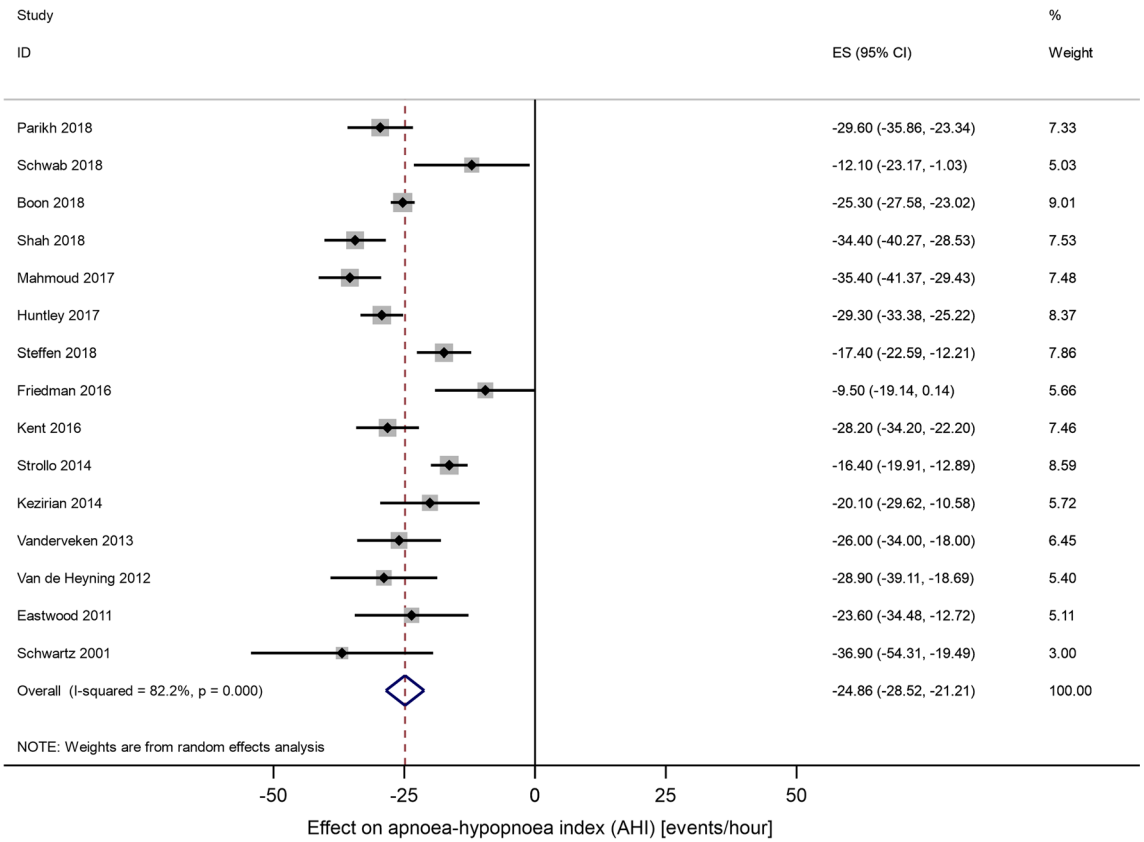

Fig 2 Forest plot on the effect of HNS on AHI

suitable for different types of OSA patients, and more research on effectiveness and responder criteria of treatment alternatives is needed.

An uncontrolled trial on a hybrid method of electrical stimulation has recently been published [35]. This technique works via a submental bilateral neurostimulator that is

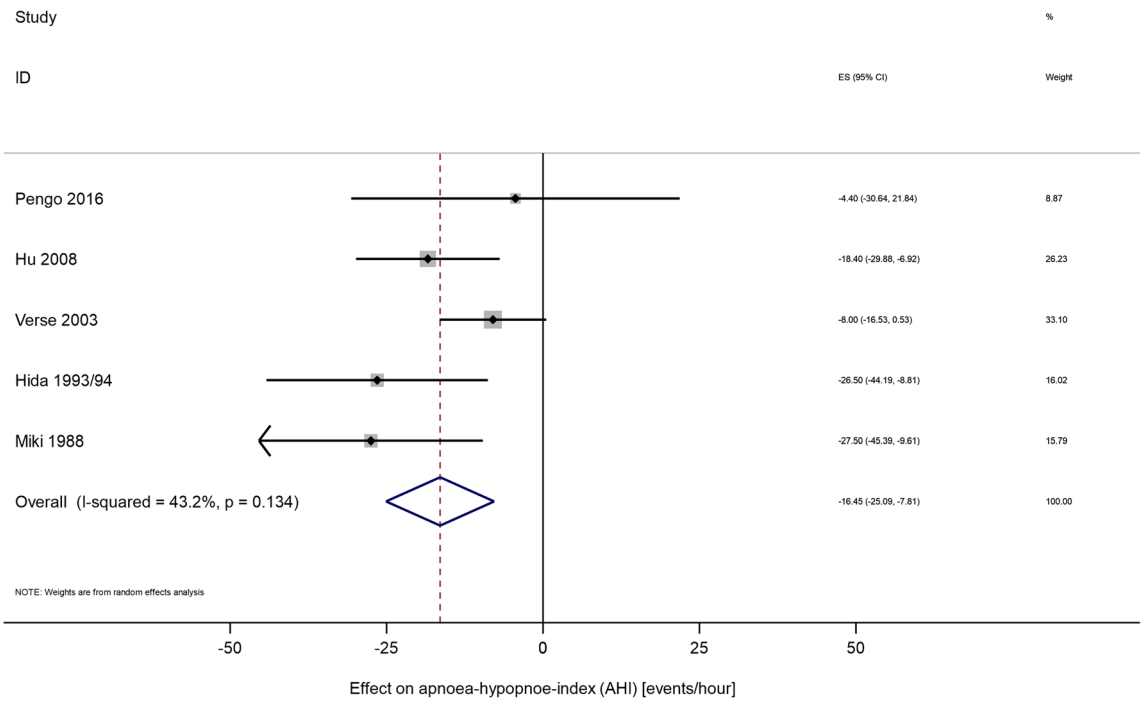

Fig 3 Forest plot on the effect of TES on AHI

Table 3 Effect of electrical stimulation on AHI, ODI and ESS

	Effect (SE)	95% CI	*p* value	I^2 statistic	Between-studyvariance (τ^2)
Apnea-hypopnea index (AHI)					
All ($n = 20$)	− 23.5	− 27.0, − 20.0	$p < 0.001$	80.3	41.6
HNS ($n = 15$)	− 24.9	− 28.5, − 21.2	$p < 0.001$	82.2	37.3
TES ($n = 5$)	− 16.5	− 25.1, − 7.8	$p < 0.001$	43.2	39.8
DISE ($n = 9$)	− 26.2	− 31.4, − 20.9	$p < 0.001$	86.6	53.6
No DISE ($n = 11$)	− 20.4	− 25.8, − 14.9	$p < 0.001$	72.4	48.4
Oxygen desaturation index (ODI)					
All ($n = 9$)	− 11.6	− 15.1, − 8.0	$p < 0.001$	37.2	8.9
HNS ($n = 6$)	− 12.4	− 16.2, − 8.7	$p < 0.001$	35.3	7.2
TES ($n = 3$)	− 7.9	− 16.6, − 0.9	$p = 0.079$	22	10.1
Epworth Sleepiness Scale (ESS)					
All ($n = 11$)	−5	− 5.9, − 4.1	$p < 0.001$	60.2	1.2

Effects of electrical stimulation on the apnea-hypopnea index (AHI), oxygen desaturation index (ODI) and Epworth Sleepiness Scale (ESS) pooling all studies, and data from studies using hypoglossal nerve stimulation (HNS) and transcutaneous electrical stimulation (TES) separately. Heterogeneity statistics are given for each random-effects meta-analysis

implanted and that can be activated from outside. This might offer advantages in terms of safety compared to HNS. However, the effect size of a reduction in AHI of 54% was lower than in HNS, although slightly higher than in TES.

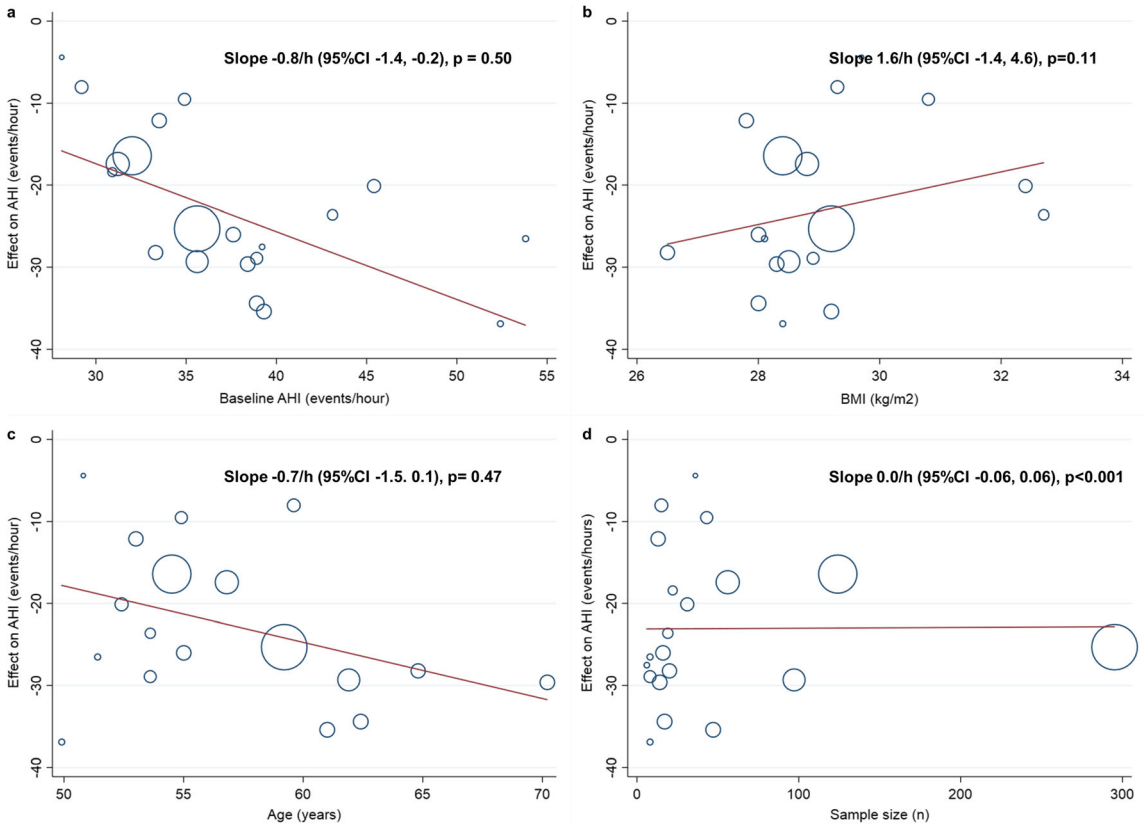

Fig 4 Association between study and patient characteristics and the effect of electrical stimulation on AHI. Plots illustrating meta-regressions to assess the effect of average patient characteristics and sample size on the effect of electrical stimulation on the apnea-hypopnea index. Association between **a** baseline AHI (h^{-1}), **b** body mass index, **c** age, and **d** sample size of each study and the treatment effect on AHI. Circles represent individual results for each study with the size of the circle being proportional to its weight in the random-effects meta-analysis. Each regression line was estimated using a random-effects linear meta-regression model.

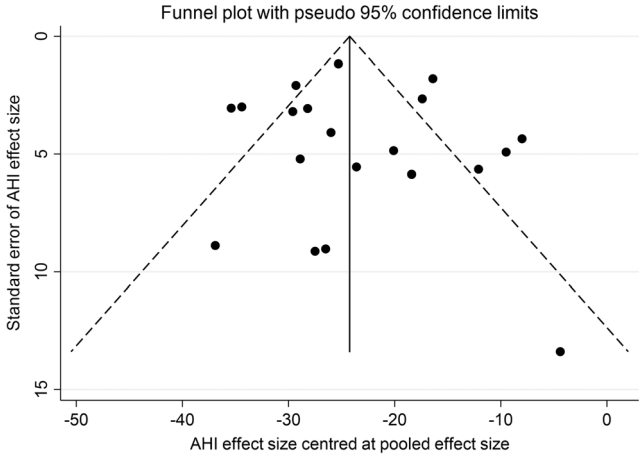

Fig 5 Funnel plot to assess publication bias. Standard error vs. effect of electrical stimulation on the apnea-hypopnea index (AHI). The solid vertical line represents the pooled treatment effect of the meta-analysis. The dots represent treatment effects estimated from individual studies (x-axis) against their standard error (y-axis). Small studies scatter more widely at the bottom. The funnel plot does not demonstrate a relevant asymmetry

MADs are an effective alternative treatment for patients who are non-compliant with CPAP or mild OSA; however, some patients do not experience any benefit at all, and others are not suitable for MADs (e.g., inappropriate dental support). CPAP can normalize the AHI in the majority of patients with OSA, while the effectiveness of electrical stimulation and MADs is more dependent on patient phenotypes. However, the reduction in the AHI using electrical stimulation demonstrated in this meta-analysis is sufficient to shift patients into a lower severity grade of OSA [36], and this could reduce symptoms and the risk of associated morbidities [37, 38].

Reductions in the ESS were previously described to be similar for both CPAP and MADs [39]. A large network meta-analysis showed CPAP to reduce ESS by 2.5 and MADs by 1.7 points [12]. HNS reduced the ESS by − 5.0 (95% CI − 5.9, − 4.1) points, which is considerably larger than the minimal clinically important difference in ESS of − 2 to − 3 [40, 41]. Currently, there are insufficient data on the effect of TES on the ESS due to lack of longer intervention periods. Assessing the impact of electrical stimulation on subjective outcomes and quality of life remains an important point for future trials on electrical stimulation [42].

The effect of HNS in this meta-analysis is comparable to previous meta-analyses based on smaller sample sizes (n = 895 in this analysis vs n = 381, 350, 200 in other meta-analyses) that found a reduction in AHI by 21.1/h and 17.5/h and in ODI to a lesser extent [43–45]. One of the previous meta-analysis [46] also included follow-up studies of the same study population at different time points that were excluded in this analysis. Constantino et al. [45] and Kompelli et al. [43] reported serious device-related adverse events in 6–11% of patients using HNS. This is the first meta-analysis comparing invasive unilateral hypoglossal nerve stimulation to non-invasive bilateral electrical stimulation of the upper airway.

HNS vs TES and responders

HNS resulted in a larger reduction of the AHI (AHI − 66%) than TES (AHI − 46%, wide confidence interval). The difference between the effect of HNS and TES was not statistically significant, but this is probably explained by the limited sample size in TES studies.

Responder criteria and the proportion of responders has not been defined and described systematically in most studies. However, if we define responder as a reduction in the AHI by > 50% to less than 10/h, we can assume that there were more non-responders to TES than to invasive HNS (absolute reduction in AHI − 66% in HNS and − 46% in TES, residual AHI 13.1/h in HNS and 19.0/h in TES based on the estimated treatment effect, different width of the confidence interval of the pooled effect of electrical stimulation on AHI). Therefore, we assume that invasive stimulation is more effective.

DISE Identifying responder criteria is essential for alternative OSA treatments to CPAP. DISE has been used for the assessment of upper airway dynamics in OSA patients under sedation [47]. Patients with anterior pharyngeal collapse respond better to HNS than patients who have multi-level or concentric obstructions [48, 49]. Interestingly, we found that the utilization of DISE had no significant impact on the effect of electrical stimulation on AHI compared to studies not using DISE; however, more of the studies not using DISE were in the non-responder range with a reduction in AHI of less than 50%.

Limitations

There is still limited evidence from RCTs using electrical stimulation in OSA. More insight on the electrical stimulation used (trigger, frequency, pulse width, waveform, polarity) is needed. Since partial upper airway reopening as a result of electrical stimulation—especially in TES—might result in a change from apneas to hypopneas or a change in duration of a respiratory events during sleep, the AHI might not be the best outcome measure. Only some trials reported effects of electrical stimulation on the ODI.

There was a high degree of heterogeneity; I^2 indicates that a high percentage in the variability of the effect size is due to heterogeneity rather than chance. This may in part be due to significant differences in the methodologies of the studies included. Meta-regressions could not identify specific sources of heterogeneity. Furthermore, the bias assessment of non-randomized studies revealed that most of the studies are at a risk of bias towards the intervention. This further emphasizes the need for well-designed future RCTs to evaluate both HNS and TES further.

Table 4 A "low risk of bias" means that this aspect was comparable to a well-performed randomized controlled trial, a "moderate risk of bias" indicates that this study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial, a "serious risk of bias" means the study had some important problems in this domain, and a "critical risk of bias" means the study is too problematic in this domain to provide any useful evidence [18]

Author year	DISE	HNS (1) TES (2)	Uncontrolled confounders	Selection	Classification of intervention	Deviation from intervention	Missing data	AHI measurement	Overall bias for AHI	Overall direction
Parikh 2018	0	1	Small sample, no controls (moderate risk)	Retrospective data (moderate risk)	Low risk	Low risk	Low risk	Low risk	*Moderate*	Favors treatment
Schwab 2018	0	1	Small sample, no controls (moderate risk)	Low risk	Low risk	Low risk	Low risk	Low risk	*Moderate*	Favors treatment
Boon 2018	0	1	No controls (moderate risk)	Retrospective data, not all implanted patients included (serious risk)	Low risk	Low risk	Low risk	AHI scoring not standard (serious risk)	*Serious*	Favors treatment
Shah 2018	1	1	35% prior UA surgery for OSA (serious risk)	Retrospective data (moderate risk)	Low risk	Low risk	Low risk	Low risk	*Serious*	Favors treatment
Mahmoud 2017	1	1	No controls, 64% UA surgery (serious risk)	Retrospective data (moderate risk)	Low risk	Low risk	Low risk	Low risk	*Serious*	Favors treatment
Huntley 2017	1	1	No controls (moderate risk)	Retrospective data (moderate risk)	Low risk	Low risk	23 dropout (moderate risk)	Low risk	*Moderate*	Favors treatment
Steffen 2018	1	1	No controls, surgeon's discretion to exclude patients (serious risk)	Consecutive recruitment (moderate risk)	Low risk	Low risk	Low risk	Low risk	*Serious*	Favors treatment
Friedman 2016	0	1	No controls, previous UA surgery (1 patient), PSG score not standardized (serious risk)	Low risk	Low risk	Low risk	Low risk	Low risk	*Serious*	Favors treatment
Kent 2016	1	1	No controls, small sample, 50% had UA surgery (serious risk)	Consecutive retrospective recruitment (moderate risk)	Low risk	Low risk	Low risk	Low risk	*Serious*	Favors treatment
Strollo 2014	1	1	No controls (moderate risk)	Low risk	Low risk	Low risk	Low risk	Low risk	*Moderate*	Favors treatment
Kezirian 2014	1	1	No controls (moderate risk)	Low risk	Low risk	Low risk	Low risk	Low risk	*Moderate*	Favors treatment
Vanderveken 2013	1	1	No controls, small sample (moderate risk)	Low risk	Low risk	Low risk	Low risk	Low risk	*Moderate*	Favors treatment
Van de Heyning 2012	1	1	No controls, small sample (moderate risk)	Known responders (serious risk)	Low risk	Low risk	Low risk	Low risk	*Serious*	Favors treatment
Eastwood 2011	0	1	No controls, small sample (moderate risk)	First 6 participants enrolled prior to defining eligibility criteria (serious risk)	Low risk	Low risk	Low risk	Low risk	*Serious*	Favors treatment
Hu 2008	0	2	No controls, small sample (moderate risk)	Low risk	Low risk	Low risk	Low risk	Low risk	*Moderate*	Favors treatment
Verse 2003	0	2	No controls, small sample (moderate risk)		Low risk	Low risk	Low risk	Low risk	*Serious*	Favors treatment

Table 4 (continued)

Author year	DISE	HNS (1) TES (2)	Uncontrolled confounders	Selection	Classification of intervention	Deviation from intervention	Missing data	AHI measurement	Overall bias for AHI	Overall direction
				Only tongue base obstruction included, limited info on selection process (serious risk)						
Schwartz 2001	0	1	No controls, small sample, 25% previous UA surgery (serious risk)	Limited info on selection process (serious risk)	Low risk	Low risk	Low risk	Low risk	*Serious*	Favors treatment
Hida 1993/94	0	2	No sample size or demographics (serious risk)	No info on selection process (serious risk)	Low risk	Low risk	Unknown (serious)	Low risk	*Serious*	Direction unclear
Miki 1988	0	2	Small sample, no demographic info (serious risk)	Limited info on selection process (serious risk)	Low risk	Low risk	Low risk	Low risk	*Serious*	Direction unclear

Conclusions

Invasive hypoglossal nerve stimulation and transcutaneous electrical stimulation of the upper airway reduce OSA severity by a clinically relevant margin, and HNS has been shown to improve associated symptoms. However, there is a lack of randomized controlled trials for HNS in OSA and for long-term follow up using TES.

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Compliance with ethical standards

Competing interests J.S. is named inventor on a patent for an apparatus to use transcutaneous electrical stimulation to treat obstructive sleep apnea and snoring (WO2016124739A1). No other conflicts of interest related to the content of the manuscript are reported.

Registration The systematic review has been registered on PROSPERO (PROSPERO 2017:CRD42017074674).

Guarantor Dr. Esther I Schwarz is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the integrity of the submission as a whole.

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