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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

Hypoglossal nerve stimulation long-term clinical outcomes: a systematic review and meta-analysis

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Abstract

Objective To perform a systematic review and meta-analysis for studies evaluating hypoglossal nerve stimulation (HNS) clinical outcomes in the treatment of moderate to severe obstructive sleep apnea (OSA).

Methods Two authors conducted a literature search to identify prospective studies in PubMed/MEDLINE, Google Scholar, and Cochrane Library databases. The last search was performed on November 17, 2018.

Results A total of 350 patients (median age 54.3 (IQR 53–56.25) years, BMI 29.8 (IQR 28.8–31.6) kg/m^2) from 12 studies were included. The procedure has obtained a surgical success rate of 72.4% (Inspire), 76.9% (ImThera), 55% (Apnex) at 12 months, and 75% (Inspire) at 60-month follow-up. At 12 months, the apnea-hypopnea index (AHI) mean differences was − 17.50 (Inspire; 95% CI: − 20.01 to − 14.98, $P < 0.001$), − 24.20 (ImThera; 95% CI: − 37.39 to 11.01, $P < 0.001$), and − 20.10 (Apnex; 95% CI: − 29.62 to − 10.58, $P < 0.001$). The AHI mean reduction after 5 years was − 18.00 (Inspire, − 22.38 to − 13.62, $P < 0.001$). The Epworth sleepiness scale (ESS) mean reduction was − 5.27 (Inspire), − 2.90 (ImThera), and − 4.20 (Apnex) at 12 months and − 4.40 (Inspire) at 60 months, respectively. Only 6% of patients reported serious device-related adverse events after 1- and 5-year follow-up.

Conclusion HNS has obtained a high surgical success rate with reasonable long-term complication rate related to the device implanted. The procedure represents an effective and safe surgical treatment for moderate-severe OSA in selected adult patients who had difficulty accepting or adhering to CPAP treatment.

Keywords Obstructive sleep apnea · Hypoglossal nerve · Upper airway · Stimulation · Long term

Introduction

Obstructive sleep apnea (OSA) represents a multifactorial chronic disorder characterized by recurrent upper airway obstruction during sleep [1, 2]. The standard for treatment is currently continuous positive airway pressure (CPAP), but unfortunately, only a portion of patients achieve a reasonable adherence to long-term treatment [3, 4]. Given the multilevel upper airway collapse [5], numerous surgical procedures with different anatomical targets have been proposed during the last years [6]. However, few surgical approaches obtain a proper clinical outcome alone [7].

Hypoglossal nerve stimulation (HNS) has been found to be a surgical therapy able to achieve responsiveness in a significant proportion of patients in this context. It is performed in patients who had difficulty accepting or adhering to CPAP treatment and who suffer from a moderate to severe disease [8, 9].

Several papers have shown that HNS leads to multilevel upper airway patency with a non-demolitive surgical procedure alone [10–12]. A prior meta-analysis [13] was conducted in 2014 to evaluate the efficacy of HNS for OSA treatment showing optimistic results. From that time, we had an exponential increase in the number of papers related to HNS with different perspectives, and long-term outcomes are, moreover, finally available. Therefore, the aim of this paper is to perform

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an updated systematic review and a meta-analysis in order to quantify HNS long-term clinical outcomes with a larger patient cohort. The study was carried out according to PICOS acronym: *Patients* (P), adults suffering from OSA; *Intervention* (I), hypoglossal nerve stimulation; *Comparison* (C), pre and post-implantation; *Outcome* (O), apnea-hypopnea index (AHI), oxygen desaturation index (ODI), Epworth sleepiness scale (ESS); *Study design* (S), only prospective studies.

Methods

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Eligibility criteria

Only prospective studies assessing the efficacy of HNS for OSA treatment in an adult population were included according to PICOS acronym previously described. Included studies needed to report at minimum AHI, ODI, and ESS outcomes. The comparison had to be between baseline and post-implantation outcomes with no restrictions according to follow-up length. No language, publication date, or publication status restrictions were imposed, but articles had to be published in a peer-reviewed journal.

Data source and study searching

We performed a thorough search for appropriate published studies in PubMed/MEDLINE, Google Scholar, and Cochrane Library databases. Relevant keywords, phrases, and MeSH terms were searched. An example of a search strategy is the one used for PubMed/MEDLINE: "sleep apnea" AND "hypoglossal nerve stimulation" OR "upper airway stimulation" OR "hypoglossal nerve surgery" OR "hypoglossal nerve therapy". The searches in the remaining databases were adjusted to fit the specific requirements for each of the individual databases. To minimize the risk of missing relevant data, a cross-reference search of the selected articles was performed, and the "cited by" function on Google Scholar was also used to obtain other relevant articles for the study. The last search was performed on November 17, 2018.

Data collection process

Two independent reviewers (A.C. and A.M.) separately conducted the search. All articles were initially screened for relevance by title and abstract, obtaining the full-text article if the abstract did not allow the investigators to assess the defined inclusion and exclusion criteria. The two investigators (A.C. and A.M.) separately reviewed the abstract of each publication and then performed a close reading of all papers to minimize selection bias and errors. The conflict between reviewers was resolved by consensus. The most updated and inclusive data for each study were chosen for abstraction.

Study quality assessment

The National Institute for Health and Clinical Excellence (NICE) quality assessment tool was used to evaluate the quality of the included studies [15].

Statistical analysis

The meta-analysis utilized pre-treatment (baseline) to post-implantation measures with all subjects serving as their own controls. Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2014) was used to calculate the magnitude of the treatment effect. I^2 was calculated as a measure of heterogeneity for the main analysis. An I^2 value represents the percentage of total variation across studies caused by heterogeneity rather than by chance. Using a fixed effects model, we assumed that all studies come from a common population and that the effect size is not significantly different among the different trials. If the heterogeneity test produced a low probability value (Q-statistic, $P < 0.05$), then a more conservative random effects model was used. A subgroup analysis was performed according to the different stimulation systems (Inspire, ImThera, and Apnex) and follow-up (6 and 12 months). Heterogeneity across subgroups was assessed with Cochran's Q method. Descriptive statistics on patients' characteristics in the studies are provided. Dichotomous variables were reported as counts and percentage, and continuous variables as mean ± standard deviation, or as median ± IQR (interquartile range) if the values were not normally distributed. Clinical measures were reported as mean ± standard deviation (SD) as provided by the individual studies. Statistical significance was defined at $P < 0.05$.

Results

Study selection

A flow chart of the study identification process is shown in Fig. 1. After duplicate removal, a total of 1063 potentially relevant publications were identified through database searching and other sources. Seventy-eight studies were potentially relevant after abstract and title review; therefore, the

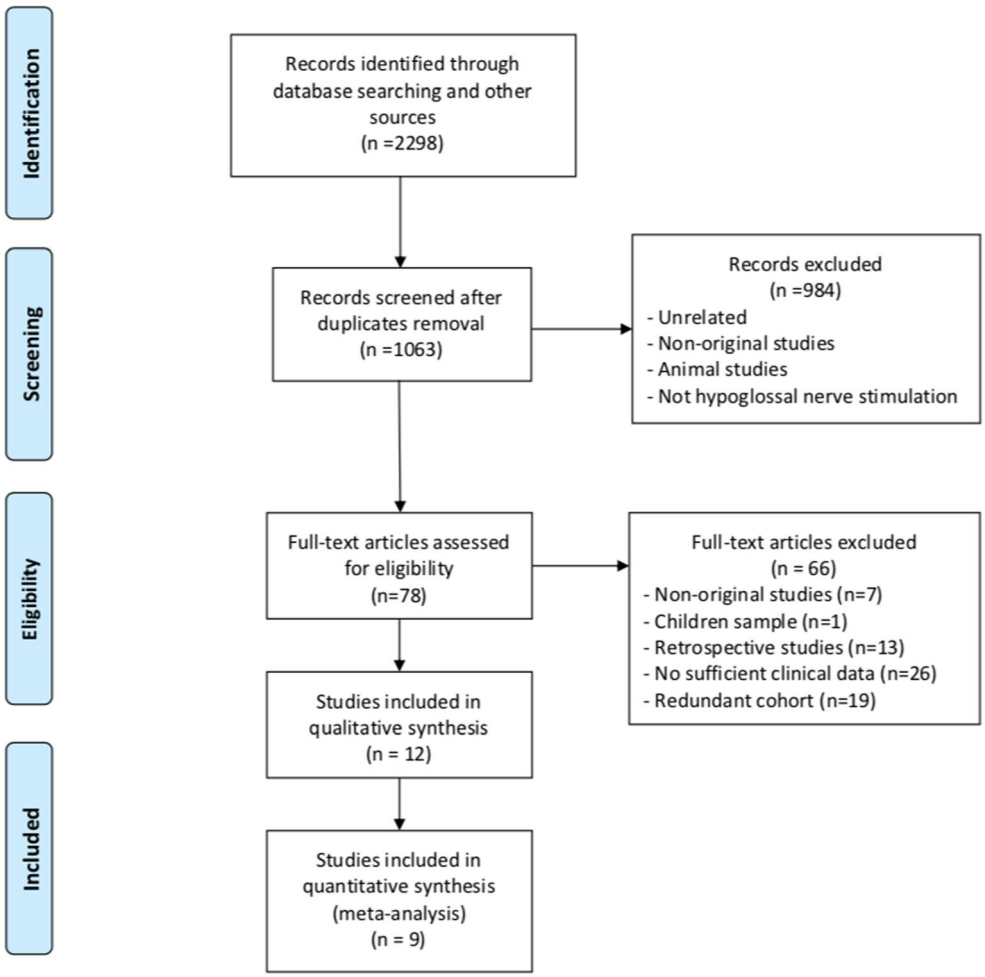

Fig. 1 PRISMA 2009 flow diagram

full-text papers were obtained for potential inclusion. After applying the inclusion criteria, 12 studies [9, 16–26] met criteria with a total of 350 patients (median age 54.3 (IQR 53–56.25) years; BMI 29.8 (IQR 28.8–31.6) kg/m^2) excluding redundant cohort of same studies with different follow-up lengths (STAR Trial [9, 20, 21, 25] and German Post-Market Study [23, 24]). According to different stimulation systems, 239 patients (age 55.7 (IQR 53.95–58.20) years; BMI 28.8 (IQR 28.65–29.35) kg/m^2), 59 patients (age 52.6 (IQR 50.3–54.9) years; BMI 30.65 (IQR 30.5–30.8) kg/m^2), 52 patients (age 53.0 (IQR 52.4–53.6) years; BMI 32.55 (IQR 32.4–32.7) kg/m^2) were implanted with Inspire, ImThera, and Apnex, respectively. The reasons behind the exclusions of 65 studies are shown in Fig. 1.

Methodological quality of included studies

All of the prospective included studies were of generally high quality and satisfied at least six of the eight NICE quality assessment tool items (Table 1). The main limitation is that the great number of studies (8/12) did not include an explicit statement that patients were recruited consecutively. In addition, only eight studies reported stratified outcomes. The other items were satisfied by the majority of the included studies. In all included studies, the American Academy of Sleep Medicine (AASM) apnea and hypopnea definitions were used [27], except that a 4% oxygen desaturation was required for a hypopnea (i.e., modified Chicago criteria). In-laboratory polysomnography (PSG) was conducted in all instances. Home sleep polygraphy data were used for one study in order to ensure a uniform comparison between baseline and postoperative AHI and ODI [22].

Outcome assessment

The clinical outcomes of each included studies are shown in Table 2. Only nine studies were included in the quantitative synthesis given that the other three papers (STAR trial) [20, 21, 25] showed a longer follow-up period (18, 36, and 60 months). We performed a stratified analysis according to the duration of follow-up (6 and 12 months) for each primary outcome (AHI, ODI, and ESS).

Table 1 Quality Assessment of case series studies checklist from National Institute for Health and Clinical Excellence: (1) Was the case series collected in more than one center (i.e., multi-center study? (2) Is the hypothesis/aim/objective of the study clearly described? (3) Are the inclusion and exclusion criteria (case definition) clearly reported? (4) Is there a clear definition of the outcomes reported? (5) Were data collected prospectively? (6) Is there an explicit statement that patients were recruited consecutively? (7) Are the main findings of the study clearly described? (8) Are outcomes stratified (e.g., by abnormal results, disease stage, patient characteristics)?

	Study's general characteristics							Quality assessment of included studies							
Author, year	Follow-up	Mean age (No. of patients)	Mean BMI	Device	Inclusion criteria	Exclusion criteria	Outcomes analyzed	1	2	3	4	5	6	7	8
Eastwood et al.,[16] 2011	6 months	53.6 ± 9.2 (21)	32.7 ± 3.6	Apnex	CPAP failure; age between 21 and 70 years; BMI ≤ 40; AHI between 20 and 100/h, with ≥ 15/h occurring in NREM sleep, predominance of hypopneas (≥ 80%).	Prior surgery on palate, tongue, mandible or maxilla; enlarged tonsils; uncontrolled nasal obstruction; severe retrognathia; > 5% central or mixed apneic events; sleep disorders other than OSA; accident secondary to excessive sleepiness; major disorder of the pulmonary, cardiac, renal or nervous systems; chronic narcotic use; another implantable device; systemic infection; major depression; pregnancy or breastfeeding.	AHI, ODI, FOSQ, ESS, SAQLI, PSQI, BDI	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Van de Heyning et al.,[17] 2012	6 months	Part I: 55.7 ± 8.1 (20); Part II: 53.6 ± 11.9 (8)	Part I: 29.8 ± 2.7 (20); Part II: 28.9 ± 2.1 (8)	Inspire	CPAP failure. Part I: BMI < 35; AHI > 25; Part II: BMI ≤ 32; 20 < AHI < 50; absence of concentric collapse.	COPD; NYHA III or IV CHF; neuromuscular diseases; prior upper airway surgeries not related to OSA.	AHI, ODI, FOSQ, ESS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Friedman et al.,[26] 2016	6 months	54.9 ± 11.1 (46)	30.8 ± 3.7	ImThera	CPAP failure; BMI ≤ 37; AHI ≥ 20.	10% CSA; enlarged tonsils (3+ or 4+); Modified Mallampati IV; nasal obstruction; syndromic craniofacial abnormalities; epiglottic obstruction; positional OSA (> 50% reduction in AHI between supine and nonsupine positions); another implantable device.	AHI, ODI, ESS, SAQLI	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Heiser et al.,[23] 2017	6 months	56.8 ± 9.1 (56)	28.8 ± 3.6	Inspire	CPAP failure; 15 < AHI < 65, central apnea < 25%.	BMI > 35; complete concentric collaps at the velopharynx; tonsils size 3+ or 4+; pregnancy; another implantable device; requirement of MRI.	AHI, ODI, ESS, FOSQ	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Kezirian et al.,[19] 2014	6–12 months	52.4 ± 9.4 (31)	32.4 ± 3.6	Apnex	CPAP failure; Age 21–70; BMI ≤ 40; 20 < AHI < 100 (15 non-REM).	Prior upper airway surgery; markedly enlarged tonsils; uncontrolled nasal obstruction; severe retrognathia; > 5% central or mixed apnoeic events; sleep disorders other than OSA; major disorder of the pulmonary, cardiac, renal, or nervous systems.	AHI, ODI, FOSQ, ESS, SAQLI, PSQI, BDI	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Heiser et al.,[22] 2016	6–12 months	59.6 ± 10.9 (31)	28.8 ± 3.1	Inspire	CPAP failure; 15 < AHI < 65, central apnea <25%.	BMI > 35; pronounced anatomical abnormalities; COPD; neuromuscular diseases; hypoglossal nerve palsy; cardiovascular disease; active psychiatric disease; requirement of MRI.	AHI, ODI, ESS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Mwenge et al.,[18] 2013	12 months	50.3 ± 10 (13)	30.5 ± 3.6	ImThera	CPAP failure; AHI > 20; 25 < BMI < 40; age 25–70;	Pregnancy; CSA; restless leg syndrome or insomnia; syndromic craniofacial	AHI, ODI, ESS, FSS	No	Yes	Yes	Yes	Yes	No	Yes	Yes

Table 1 (continued)

	Study's general characteristics							Quality assessment of included studies							
Author, year	Follow-up	Mean age (No. of patients)	Mean BMI	Device	Inclusion criteria	Exclusion criteria	Outcomes analyzed	1	2	3	4	5	6	7	8
					Mallampati 1–3; Palatine tonsils grade 0–2.	abnormality; palatine tonsils grade 3–4; Mallampati score IV; obstructive nasal polyps; psychiatric disorders.									
Steffen et al.,[24] 2017	12 months	56.8 ± 9.1 (56)	28.8 ± 3.6	Inspire	CPAP failure; 15 < AHI < 65, central apnea < 25%.	BMI > 35; complete concentric collaps at the velopharynx; tonsils size 3+ or 4+; pregnancy; another implantable device; requirement of MRI.	AHI, ODI, ESS, FOSQ	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Strollo et al.,[9] 2014	12 months	54.3 ± 10.2 (124)	28.5 ± 2.6	Inspire	CPAP failure; 20 < AHI < 50	Central or mixed apnea > 25%; nonsupine AHI < 10; BMI > 32.0; neuromuscular disease; hypoglossal-nerve palsy; major disorder of the pulmonary, cardiovascular systems; psychiatric disease; nonrespiratory sleep disorders.	AHI, ODI, ESS, FOSQ	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Strollo et al.,[20] 2015	18 months	54.3 ± 10.2 (123)	28.5 ± 2.6	Inspire	CPAP failure; 20 < AHI < 50	Central or mixed apnea > 25%; nonsupine AHI < 10; BMI > 32.0; neuromuscular disease; hypoglossal-nerve palsy; major disorder of the pulmonary, cardiovascular systems; psychiatric disease; nonrespiratory sleep disorders.	AHI, ODI, ESS, FOSQ	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Woodson et al.,[21] 2015	36 months	54.3 ± 10.3 (113)	28.6 ± 2.6	Inspire	CPAP failure; 20 < AHI < 50	Central or mixed apnea > 25%; nonsupine AHI < 10; BMI > 32.0; neuromuscular disease; hypoglossal-nerve palsy; major disorder of the pulmonary, cardiovascular systems; psychiatric disease; nonrespiratory sleep disorders.	AHI, ODI, ESS, FOSQ	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Woodson et al.,[25] 2018	60 months	54.4 ± 10.3 (92)	28.6 ± 2.5	Inspire	CPAP failure; 20 < AHI < 50	Central or mixed apnea > 25%; nonsupine AHI < 10; BMI > 32.0; neuromuscular disease; hypoglossal-nerve palsy; major disorder of the pulmonary, cardiovascular systems; psychiatric disease; nonrespiratory sleep disorders.	AHI, ODI, ESS, FOSQ	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

BMI body mass index, *AHI* apnea-hypopnea index, *ODI* oxygen desaturation index, *ESS* Epworth sleepiness scale, *FOSQ* Functional Outcomes of Sleep Questionnaire, *SAQLI* Sleep Apnea Quality of Life Index, *PSQI* Pittsburgh Sleep Quality Index, *BDI* Beck Depression Index, *CSA* central sleep apnea, *COPD* chronic obstructive pulmonary disease, *CHF* congestive heart failure

Table 2 The clinical outcomes of each included studies

Author, year	Follow-up, No. of patients	AHI-pre	AHI-post	ODI-pre	ODI-post	ESS-pre	ESS-post	Secondary outcomes	Adherence (h per night)	Success rate[a]
Eastwood et al.,[16] 2011	6 months, 21	43.1 ± 17.5	19.5 ± 16.7	16.8 ± 14.4	9.1 ± 16.7	12.1 ± 4.7	8.1 ± 4.4	FOSQ-pre = 14.4 ± 2.0, FOSQ-post = 16.7 ± 2.2; SAQLI-pre = 3.2 ± 1.0, SAQLI-post = 4.9 ± 1.3; PSQI-pre = 10.1 ± 2.6, PSQI-post = 8.7 ± 3.9; BDI-pre = 15.8 ± 9.0, BDI-post = 9.7 ± 7.6.	5.8 ± 1.6 h	67%
Van de Heyning et al.,[17] 2012	6 months, 20 (Part I)	43.6 ± 18.4	41.6 ± 16.7	30.1 ± 24.0	33.5 ± 20.3	11.0 ± 5.0	7.6 ± 4.3	FOSQ-pre = 89.1 ± 23.5, FOSQ-post = 100.8 ± 16.9	–	30%
	6 months, 8 (Part II)	38.9 ± 9.8	10 ± 11	32.1 ± 15.1	9.5 ± 10.2				–	87.50%
Friedman et al.,[26] 2016	6 months, 46	34.9 ± 22.5	25.4 ± 23.1	32.4 ± 22.3	23.6 ± 22.3	12.0 ± 4.8	8.3 ± 4.4	SAQLI-pre = 4.3 ± 1.0, SAQLI-post = 4.7 ± 1.2	–	35%
Heiser et al.,[23] 2017	6 months, 56	31.2 ± 13.2	12 ± 9.8	27.6 ± 16.4	13.5 ± 10.7	12.8 ± 5.4	7 ± 4.5	FOSQ-pre = 13.2 ± 3.5, FOSQ-post = 16.9 ± 2.9	6.1 ± 1.7 h	68%
Kezirian et al.,[19] 2014	6 months, 31	45.4 ± 17.5	20.8 ± 17.6	20.9 ± 17.3	10.7 ± 17.1	12.1 ± 4.6	8.3 ± 3.6	FOSQ-pre = 14.2 ± 2.0, FOSQ-post = 16.8 ± 2.4; SAQLI-pre = 3.2 ± 1.0, SAQLI-post = 4.8 ± 1.4; PSQI-pre = 9.9 ± 3.2, PSQI-post = 8.3 ± .4.3; BDI-pre = 15.7 ± 9.0, BDI-post = 8.5 ± .7.8.	5.4 ± 1.4 h (9 months)	55%
	12 months, 31	45.4 ± 17.5	25.3 ± 20.6	20.9 ± 17.3	15.7 ± 19.6	12.1 ± 4.6	7.9 ± 3.8	FOSQ-pre = 14.2 ± 2.0, FOSQ-post = 17.0 ± 2.4; SAQLI-pre = 3.2 ± 1.0, SAQLI-post = 4.9 ± 1.4; PSQI-pre = 9.9 ± 3.2, PSQI-post = 7.8 ± 4.3; BDI-pre = 15.7 ± 9.0, BDI-post = 9.1 ± 8.2.	–	55%
Heiser et al.,[22] 2016	6 months, 31	26.3 ± 12.9	7.6 ± 5.3	28.4 ± 13.1	11.7 ± 8.8	12.6 ± 5.6	5.9 ± 4.8	–	6.0 ± 2.2 h	96.80%
	12 months, 31	26.3 ± 12.9	7.1 ± 5.9	28.4 ± 13.1	9.9 ± 8	12.6 ± 5.6	5.9 ± 5.2	–	6.6 ± 2.7 h	96.80%
Mwenge et al.,[18] 2013	12 months, 13	45.2 ± 17.8	21 ± 16.5	29.2 ± 19.6	15.3 ± 16.2	10.8 ± 6.2	7.9 ± 4.2	–	–	76.90%
Steffen et al.,[24] 2017	12 months, 56	31.2 ± 13.2	13.8 ± 14.8	27.6 ± 16.4	13.7 ± 14.9	12.8 ± 5.4	6.5 ± 4.5	FOSQ-pre = 13.7 ± 3.6, FOSQ-post = 17.5 ± 3.0	5.6 ± 2.1 h	73%
Strollo et al.,[9] 2014	12 months, 124	32 ± 11.8	15.3 ± 16.1	28.9 ± 12	13.9 ± 15.7	11.6 ± 5	7 ± 4.2	FOSQ-pre = 14.3 ± 3.2, FOSQ-post = 17.3 ± 2.9	–	66%
Strollo et al.,[20] 2015	18 months, 123	32.0 ± 11.8	14.1 ± 14.4	28.9 ± 12.0	12.7 ± 13.5	11.6 ± 5.0	7.0 ± 4.0	FOSQ-pre = 14.3 ± 3.2, FOSQ-post = 17.3 ± 3.0	–	64%
Woodson et al.,[21] 2015	36 months, 113	30.4 ± 10.4	11.5 ± 13.9	27.1 ± 10.8	9.1 ± 11.7	11.4 ± 5.1	7.0 ± 5.0	FOSQ-pre = 14.6 ± 3.0, FOSQ-post = 17.4 ± 3.5	–	74%
Woodson et al.,[25] 2018	60 months, 92	30.4 ± 9.4	12.4 ± 16.3	27.2 ± 10.0	9.9 ± 14.5	11.3 ± 5.2	6.9 ± 4.7	FOSQ-pre = 14.7 ± 2.9, FOSQ-post = 18.0 ± 2.2	–	75%

[a] Calculated according to Sher criteria (50% reduction in AHI and overall AHI < 20)

AHI apnea-hypopnea index, *ODI* oxygen desaturation index, *ESS* Epworth sleepiness scale, *FOSQ* Functional Outcomes of Sleep Questionnaire, *SAQLI* Sleep Apnea Quality of Life Index, *PSQI* Pittsburgh Sleep Quality Index, *BDI* Beck Depression Index

Quantitative analysis

Apnea-hypopnea index

We used a random effect modeling for 6-month (Q-statistic, $P = 0.004$; $I^2 = 68\%$) follow-up data. A fixed effect modeling was used for 12-month (Q-statistic, $P = 0.77$; $I^2 = 0\%$) follow-up data.

According to 6-month subgroup analysis, the AHI mean difference was − 17.74 (Inspire; 95% confidence interval [CI]: − 24.73 to − 10.14, Z score = 4.97, $P < 0.001$), − 9.50 (ImThera; 95% CI: − 19.14 to 0.14, Z score = 1.93, $P = 0.05$), and − 24.20 (Apnex; 95% CI: − 30.94 to − 17.45, Z score = 8.67, $P < 0.001$). The combined subgroup weighted means for AHI decrease were 55.1% (Inspire), 27% (ImThera), and 54.4% (Apnex). A significant heterogeneity was found across subgroups with a $I^2 = 67.3\%$ (Q-statistic, $P = 0.05$) (Fig. 2a).

At 12 months, the subgroup analysis showed a AHI mean difference of − 17.50 (Inspire; 95% CI: − 20.01 to − 14.98, Z score = 13.64, $P < 0.001$), − 24.20 (ImThera; 95% CI: − 37.39 to 11.01, Z score = 3.59, $P < 0.001$), and − 20.10 (Apnex; 95% CI: − 29.62 to − 10.58, Z score = 4.14, $P < 0.001$). The subgroups combined weighted means for AHI decrease were

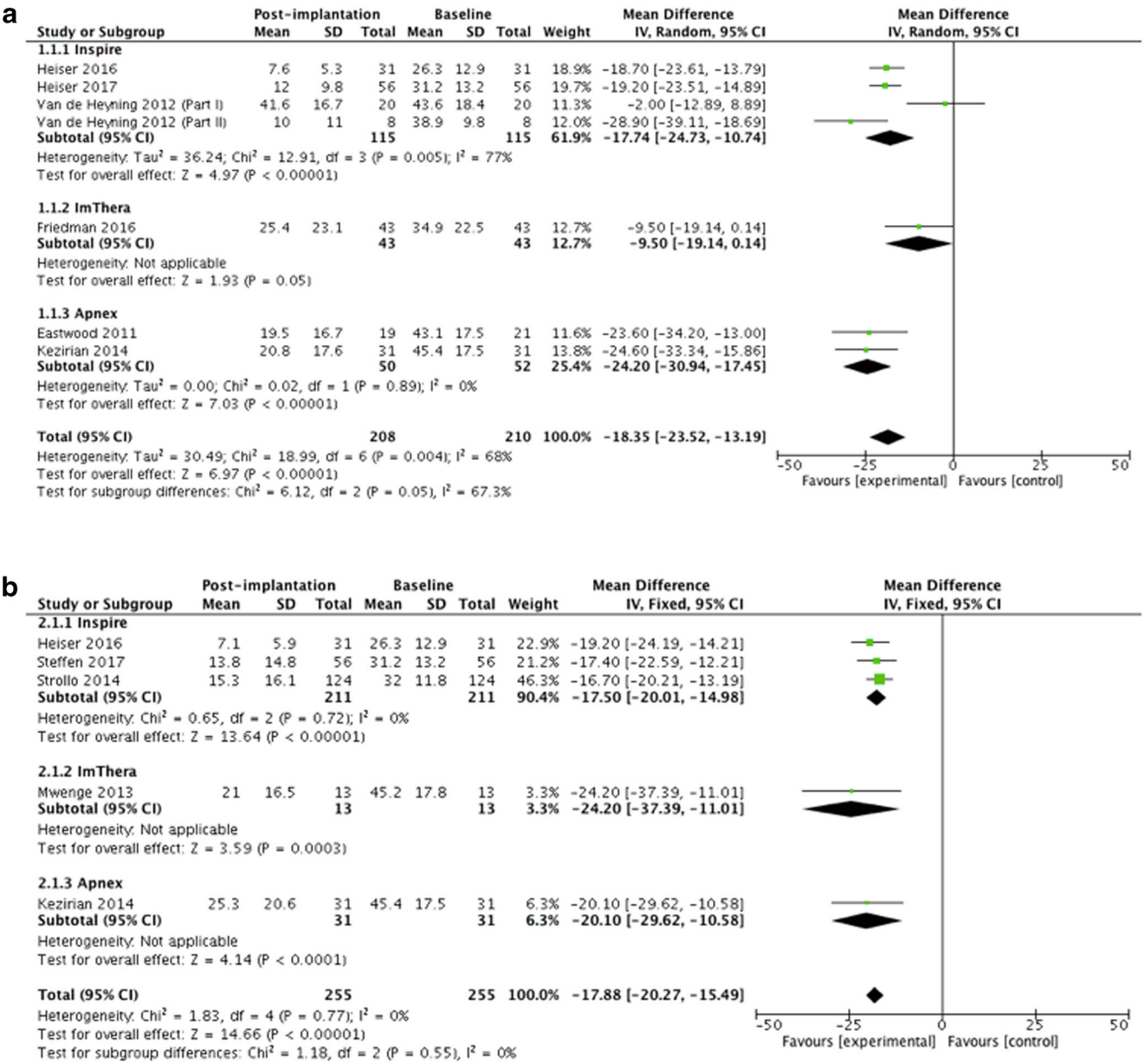

Fig. 2 Forest plot showing mean apnea-hypopnea index after hypoglossal nerve stimulation at 6-month (**a**) and 12-month (**b**) follow-up. Abbreviations: CI, confidence interval; IV, independent variable; SD, standard deviation

56.2% (Inspire), 53.5% (ImThera), and 44.3% (Apnex). No significant variability was found across subgroups with a I^2 = 0% (Q-statistic, P = 0.55) (Fig. 2b).

Oxygen desaturation index

The pooled effect analysis is shown in Fig. 3. We used a fixed effect modeling for 6- and 12-month follow-up data with a I^2 = 49% (Q-statistic, P = 0.07) and I^2 = 34% (Q-statistic, P = 0.19), respectively.

The subgroup analysis at 6 months revealed an ODI mean reduction of − 14.65 (Inspire; 95% CI: − 18.15 to − 11.16, Z score = 8.22, P < 0.001), − 8.80 (ImThera; 95% CI: − 18.23 to 0.63, Z score = 1.83, P = 0.07), and − 9.11 (Apnex; 95% CI: − 15.53 to − 2.68, Z score = 2.78, P = 0.005). The subgroups combined weighted means for ODI decrease were 43.7% (Inspire), 27.2% (ImThera), and 47.6% (Apnex).

No significant variability was found across subgroups with a I^2 = 34.1% (Q-statistic, P = 0.22) (Fig. 3a).

According to 12-month subgroup analysis, the ODI mean difference was − 15.59 (Inspire; 95% CI: − 18.21 to − 12.98, Z score = 11.70, P < 0.001), − 13.90 (ImThera; 95% CI: − 27.72 to − 0.08, Z score = 1.97, P = 0.05), and − 5.20 (Apnex; 95% CI: − 14.40 to 4.00, Z score = 1.11, P = 0.27). The subgroups combined weighted means for ODI decrease were 53.4% (Inspire), 47.6% (ImThera), and 24.9% (Apnex). No

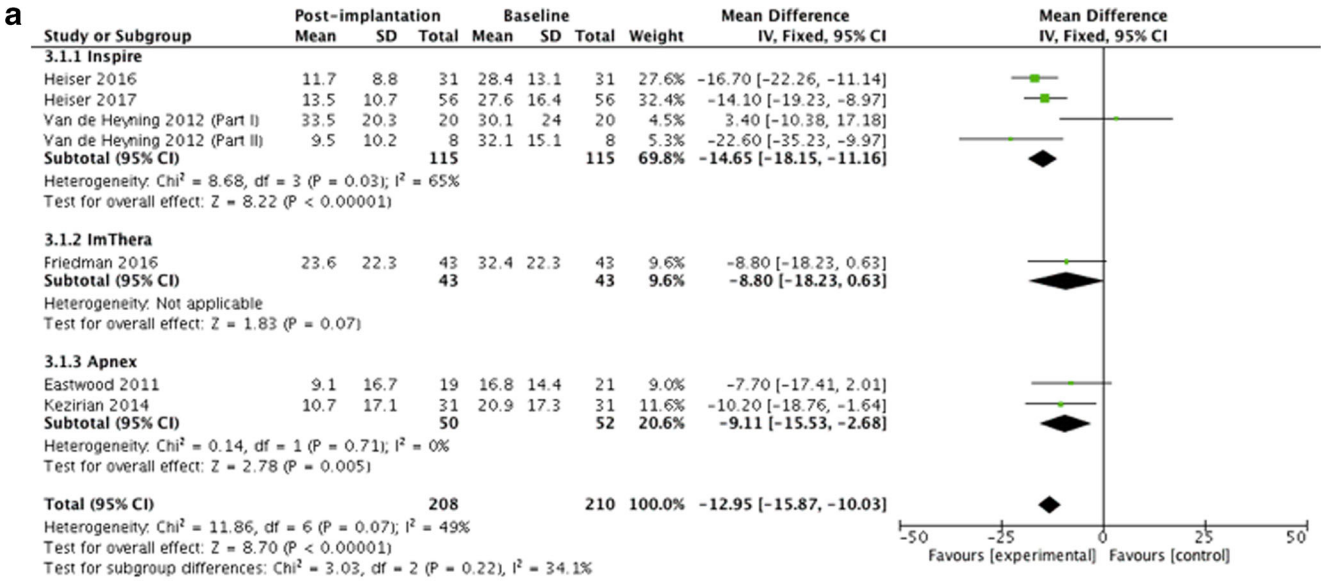

Fig. 3 Forest plot showing mean oxygen desaturation index after hypoglossal nerve stimulation at 6-month (**a**) and 12-month (**b**) follow-up. Abbreviations: CI, confidence interval; IV, independent variable; SD, standard deviation

significant heterogeneity was found across subgroups with a $I^2 = 56.1\%$ (Q-statistic, $P = 0.10$) (Fig. 3b).

Epworth sleepiness scale

The pooled effect analysis is presented in Fig. 4. We used a fixed effect modeling for both 6-month (Q-statistic, $P = 0.25$; $I^2 = 25\%$) and 12-month (Q-statistic, $P = 0.24$; $I^2 = 27\%$) follow-up data.

At 6 months, the meta-analysis revealed a statistically significant reduction in ESS mean difference of − 5.36 (Inspire; 95% CI: − 6.64 to − 4.08, Z score = 8.21, $P < 0.001$), − 3.70 (ImThera; 95% CI: − 5.65 to −1.75, Z score = 3.73, $P < 0.001$), and − 3.87 (Apnex; 95% CI: − 5.53 to − 2.21, Z score = 4.56, $P < 0.001$) (Fig. 4a). At 12 months, the ESS mean reduction was − 5.27 (Inspire; 95% CI: − 6.18 to − 4.35, Z score = 11.26, $P < 0.001$), − 2.90 (ImThera; 95% CI: − 6.97 to 1.17, Z score = 1.40, $P = 0.16$), and − 4.20 (Apnex; 95% CI: − 6.30 to − 2.10, Z score = 3.92, $P < 0.001$) (Fig. 4b).

The STAR trial long-term outcomes

Three studies [20, 21, 25] reported the HNS long-term polysomnographic data with an 18-, 36-, and 60-month follow-up,

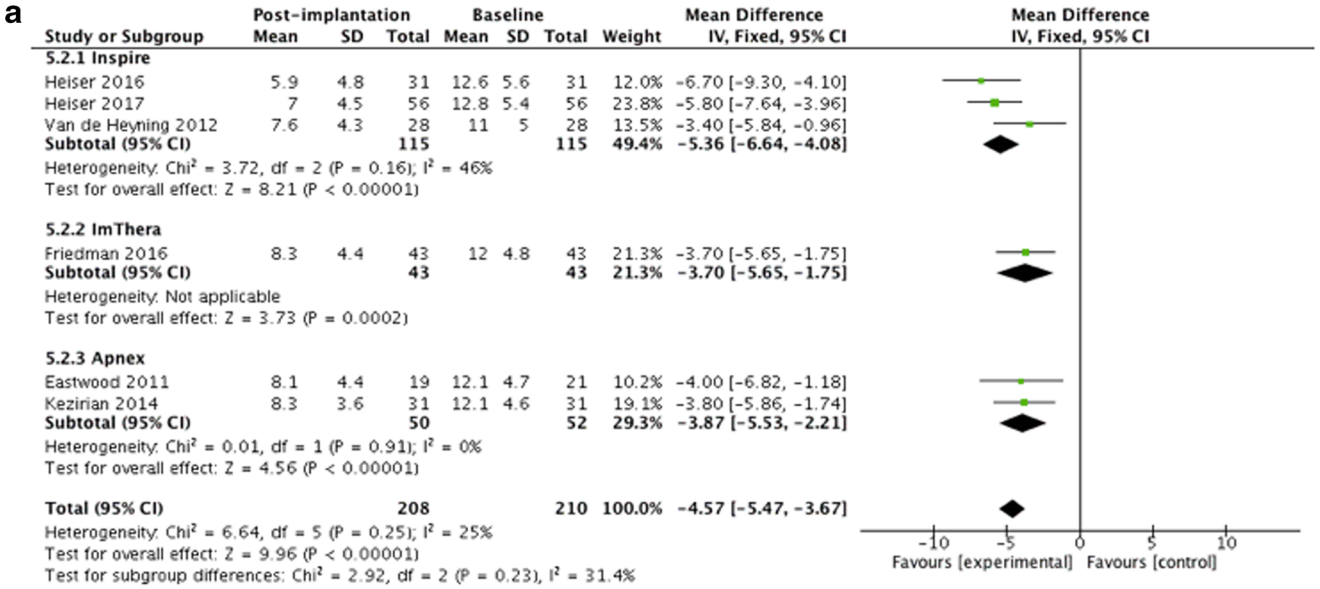

Fig. 4 Forest plot showing the Epworth sleepiness scale after hypoglossal nerve stimulation at 6-month (**a**) and 12-month (**b**) follow-up. Abbreviations: CI, confidence interval; IV, independent variable; SD, standard deviation

respectively. The AHI mean ± standard deviation decreased from 32.0 ± 11.8/h to 14.1 ± 14.4/h (18 months, $n = 123$), 30.4 ± 10.4/h to 11.5 ± 13.9/h (36 months, $n = 98$), and 30.4 ± 9.4/h to 12.4 ± 16.3/h (60 months, $n = 71$). The mean AHI was reduced by 55.9%, 62.2%, and 59.2% at 18, 36, and 60 months, respectively.

The ODI decreased from 28.9 ± 12.0/h to 12.7 ± 13.5/h (18 months, $n = 123$), 27.1 ± 10.8/h to 9.1 ± 11.7/h (36 months, $n = 98$), and 27.2 ± 10.0/h to 9.9 ± 14.5/h (60 months, $n = 71$).

The same studies indicated patients' self-reported outcome measures according to ESS and FOSQ scores. The ESS improved from 11.6 ± 5.0 to 7.0 ± 4.0 (18 months, $n = 123$), 11.4 ± 5.1 to 7.0 ± 5.0 (36 months, $n = 113$), and 11.3 ± 5.2 to 6.9 ± 4.7 (60 months, $n = 92$). The FOSQ increased from 14.3 ± 3.2 to 17.3 ± 3.0 (18 months, $n = 123$), 14.6 ± 3.0 to 17.4 ± 3.5 (36 months, $n = 113$), and 14.7 ± 2.9 to 18.0 ± 2.2 (60 months, $n = 92$).

Complication rate

According to the STAR trial, serious adverse events were defined as any events that led to death, life-threatening illness, permanent impairment, or new or prolonged hospitalization with serious health impairment [9]. Most of the included studies reported HNS non-serious complications making a distinction between procedure-related adverse events (e.g., post-operative discomfort, temporary tongue weakness, and intubation effects) and device-related adverse events (e.g., stimulation discomfort, tongue abrasion, and dry mouth).

After 5 years, only 6% of the STAR trial cohort (8/126 patients) had serious device-related adverse events requiring surgical repositioning or replacement of the neurostimulator or implanted leads. According to non-serious device-related complications, the most common adverse event recorded was discomfort due to electrical stimulation ($n = 76$, 60.3%) occurring 81 times during the first year and only 5 times during the fifth year. In addition, tongue abrasion from tongue movement ($n = 34$, 27%) was reported 28 times the first year and was reduced to 2 times during the fifth year. According to non-serious procedure-related complications, the most common adverse event reported was discomfort related to ($n = 52$, 30.2%) or independent of ($n = 42$, 27%) incision. In addition, 23 patients (18.3%) showed temporary tongue weakness after the procedure.

Other seven studies [16–19, 23, 24, 26] ($n = 195$) included in this meta-analysis reported a comparable complication rate at 6 and 12 months. Only 14 serious adverse events occurred in 12 patients (6.1%) treated. At least 1 adverse event related to implantation procedure or device was reported in 81 patients (41.5%) and 56 (28.7%), respectively.

Success rate and adherence

All nine studies included in the quantitative synthesis showed surgical success according Sher criteria (50% reduction in AHI and overall AHI < 20). The overall subgroup success rate was 70% (Inspire, $n = 115$), 35% (ImThera, $n = 46$), and 59.8% (Apnex, $n = 115$) at 6 months and 72.4% (Inspire, $n = 211$), 76.9% (ImThera, $n = 13$), and 55% (Apnex, $n = 31$) at 12 months. The STAR trial long-term surgical success rate was 64% ($n = 123$), 74% ($n = 113$), and 75% ($n = 71$) at 18, 36, and 60 months, respectively.

Five studies [16, 19, 22–24] ($n = 139$) reported therapy adherence data showing a median usage of 5.8 [IQR 5.5–6.2] h per night. According to the STAR trial cohort, participant self-reports of nightly device use were 86%, 81%, and 80% at years 1, 3, and 5, respectively.

Discussion

This meta-analysis showed how the hypoglossal nerve stimulation represents an effective and safe surgical procedure for adult patients suffering from moderate to severe OSA. All primary outcomes showed a significant improvement. HNS has resulted in an AHI reduction of 56.2% (Inspire), 53.5% (ImThera), and 44.3% (Apnex) at 12 months and 59.2% (Inspire) at 60 months, respectively, with a surgical success rate of 72.4% (Inspire), 76.9% (ImThera), and 55% (Apnex) at 12 months and 75% (Inspire) at 60 months according to Sher criteria. Similarly, the ODI has shown a reduction of 53.4% (Inspire), 47.6% (ImThera), and 24.9% (Apnex) at 12 months and 63.6% (Inspire) at 60 months, respectively. Self-reported outcome measures followed the same trend with an ESS mean reduction of − 5.27 (Inspire), − 2.90 (ImThera), and − 4.20 (Apnex) at 12 months and − 4.40 (Inspire) at 60 months, respectively. These data showed that the optimal clinical improvement obtained at 12-month follow-up is maintained after 5 years. In addition, HNS has shown to be a safe surgical procedure with a low rate of serious adverse events such as life-threatening illness, permanent impairment, or new or prolonged hospitalization with serious health impairment. In particular, only 6% of patients required surgical repositioning or replacement of the neurostimulator or implanted leads after 5 years. Even though several patients suffered from minor adverse event procedure- or device- related (e.g., discomfort due to electrical stimulation, tongue abrasion, temporary tongue weakness), these were non-serious and almost all patients achieved a full recovery. Moreover, the long follow-up showed that device-related event rate progressively reduced with only a few cases during the fifth year.

A model-based health-economic projection was developed in order to predict the HNS long-term clinical- and cost-effectiveness on the basis of the STAR trial 12-month

follow-up [28]. However, this economic projection model should be corroborated by other analysis, and it remains to be seen whether a real long-term cost saving exists.

One important retrospective and prospective study not included in this meta-analysis is a large multicenter observational registry (ADHERE registry [29]) including 508 patients treated with the Inspire Medical System® device. This study has reported comparable data about HNS clinical outcomes and complication rate both at the post-titration visit (mean follow-up of 134 days) and at the final visit (mean follow-up of 386). The AHI decreased from 36.3 to 10.2 events per hour at the post-titration office visit ($n = 377$) and from 36.3 to 10.3 events per hour at the final office visit ($n = 227$), with a surgical success rate of 92% and 81%, respectively. The majority (98%) of the 508 implanting procedures were completed without an adverse event. In addition, only 23% of patients reported adverse event during the follow-up period and only one patient required a revision procedure for a dislodged stimulation cuff.

As extensively highlighted in CPAP therapy, the long-term treatment outcome is closely dependent on patients' compliance and adherence [3, 4]. The 5-year adherence data showed that HNS is associated with great nightly device use, with a patient self-report usage of 86%, 81%, and 80% at years 1, 3, and 5, respectively. Unfortunately, objective data about device use during the STAR trial were not directly reported. Only the average stimulation time per night was measured, and the estimated usage time per night was approximately 5 h. However, a median use of 5.8 h per night ($n = 139$) was reported in other studies with a follow-up of 6–12 months. These results must moreover be seen in an optimistic view considering that one of the most important inclusion criteria for HNS treatment was the CPAP non-adherence.

In relation to this issue, numerous surgical procedures were proposed for the aim of making patient CPAP independent [6], but unfortunately, these surgical approaches proposed for OSA treatment are not always able to achieve an optimal polysomnographic and self-reported improvement [7]. In addition, although other surgical procedures are able to obtain a clinical outcome comparable to HNS, it is not uncommon that OSA patients undergo several surgical procedures according to a multi-level surgical approach, with a not negligible discomfort related to repeated hospitalization and, sometimes, a more invasive and demolitive surgery [30]. Our meta-analysis showed how HNS could represent a single surgical procedure able to obtain a considerable improvement in objective and subjective clinical outcomes. Moreover, HNS is an elective surgery applied for selected patients who have failed other therapies and therefore more difficult to treat. The reason for these optimal results could be related to the achievement of airway patency at the tongue base and at the palate levels thanks to the coupling effect of the superior pharyngeal constrictor and palatoglossal muscles [11]. Although this mechanism still needs to be proven, during the stimulation of the hypoglossal nerve, a bilateral protrusion of the tongue base is accompanied by a better opening of the soft palate [31]. In the context of an increasingly widespread multilevel surgical approach [30, 32], this coupling effect and the resultant optimal clinical improvement could potentially prevent further surgical procedures. A recent retrospective study conducted by Steffen et al. [33] highlighted that uvulopalatopharyngoplasty, accompanied by tonsillectomy (UPPP-TE), could be considered for an additional soft palate surgery in patients treated with HNS; this procedure could be performed in patients with a non-optimal HNS clinical outcome and a persistent obstruction at the level of velum and oropharynx identified during the post-implantation sleep endoscopy. On the other hand, there is no indication for patients to routinely undergo UPPP-TE prior to UAS implantation given the high HNS response in patients with untreated soft palate. In addition, HNS is able to obtain a patient symptomatic improvement without an excessively demolitive procedure: aside from a few cases, the hospitalization lasts only one night and patients are discharged the day following the procedure [9].

Although this meta-analysis confirms that HNS is an effective OSA treatment, findings emerged from the subgroup analysis showed that there are not enough data to compare clinical outcomes of the different stimulation systems with strong evidence. The Inspire Medical System® was implanted in the majority of patients (68%) included in our review with a success rate of 72.4% (12 months) and 75% (60 months). The main advantage of this device, characterized by triggered (phasic) hypoglossal nerve stimulation, is that all patients go through the same strict implant protocol relative to selection, implantation, and activation with a better outcome reproducibility. In contrast, only 18% of patients were treated using the ImThera Aura6000 System® performing a targeted HNS with a continuous (tonic) stimulation pattern. In addition, the largest patient cohort [23] ($n = 46$) included in our meta-analysis was a feasibility study with a surgical success rate of only 35%. These outcomes should not be seen from a pessimist perspective because are absolutely comparable to Inspire feasibility study (success rate of 30%) [17]. Moreover, the ImThera device is small, easy to implant, and does not require a third implantable component or respiratory sensing. For this reason, further ImThera clinical outcomes should be assessed to clarify the role of this device in HNS. In addition, our review highlights even more clearly that further prospective studies comparing various stimulation devices in a single patient sample, with the same inclusion criteria and a strict implant protocol, are surely desirable in order to put this therapy on a higher level of evidence.

This systematic review has some limits.

First, the STAR trial is actually the only prospective patient cohort with a follow-up longer than 12 months. In addition,

only the 57% ($n = 71$) of the STAR trial cohort completed the 5-year polysomnographic study. Compared to the previous meta-analysis, there has been a significant expansion of HNS-related paper, but only a few prospective studies were published. The majority of papers were related to HNS features different from primary clinical outcomes (AHI, ODI, and ESS), frequently with previously published data. Although surgical clinical outcomes are comparable between 12 and 60 months, additional prospective studies with a follow-up longer than 1 year should be performed in the future.

Second, the majority of patients included in this review were treated in highly specialized centers. Despite 96% of patients were included in multicenter studies (including also some non-academic centers), it would be very interesting to obtain specific prospective data from other surgeons and in a non-academic setting. In this respect, a retrospective paper published in 2018 showed HNS outcomes of only 22 patients treated in a non-academic hospital and clinic settings [34]. The results were absolutely comparable to our data, confirming how the complication rate and clinical outcomes of this procedure are not influenced by the surgeon and center experience as previously described [35, 36]. On the other hand, we have to consider that patient selection, post-operative care, and device titration require a high level of competence that only specialized centers could provide.

Third, all studies included were prospective single-arm cohort studies. There is no currently available randomized controlled trial that compares HNS to CPAP or other surgical therapies. In addition, the majority of patients ($n = 237$; 72%) were not recruited consecutively. According to this quality parameter, we would like to emphasize that HNS is actually an elective surgery, and all patients have to accept the treatment protocol before the implantation. For this reason, consecutive recruitment could not be always ensured in prospective studies. Even though the overall results are excellent, we advise an optimization with regard to the study methodology in order to reduce the risk of bias.

Finally, we highlight that STAR trial polysomnographic data represents the best values obtained from an overnight PSG and not an entire night's measurement. It was argued that a full night study needs to be used to assess PSG outcomes to avoid an overestimated surgical success rate [37]. For this reason, we need to take account of this methodological issue while analyzing these data.

Conclusion

Given the sub-optimal adherence to CPAP, numerous surgical procedures have been proposed for the OSA. In this context, our data revealed that HNS is a promising treatment for OSA patients who had difficulty accepting or adhering to CPAP treatment. HNS long-term clinical outcomes have confirmed that HNS maintains an optimal objective and subjective improvement without long-term complications related to the device implanted. Although further prospective studies with longer follow-up and comparing various stimulation systems should be performed, these findings reveal that HNS is an excellent long-term treatment for moderate-severe OSA.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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