HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Upper airway stimulation for moderate-to-severe sleep apnea

2. Update 2022

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Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the AIHTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the AIHTA.

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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Content

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List of abbreviations

AE..... Adverse event
AHI..... Apnea hypopnea Index
C ..... Comparator
CGI-I..... Clinical global impression improvement
CI..... Confidence interval
CoI..... Conflict of interest
CPAP..... Continuous positive airway pressure
DISE..... Drug-induced sleep endoscopy
ESS ..... Epworth sleepiness scale
FOSQ ..... Functional outcomes of sleep questionnaire
FU ..... Follow-up
HAT ..... Hypoxemia time
H(G)NS..... Hypoglossal nerve stimulation
I..... Intervention
nRCT..... Non-randomised controlled trail
ODI ..... Oxygen desaturation index
OSA ..... Obstructive sleep apnea
Pt ..... Patient
PSG ..... Polysomnography
PSS ..... Patient satisfaction score
RoB..... Risk of Bias
RCT..... Randomised controlled trail
SADE ..... Serious adverse device event
SAE..... Serious adverse event
THN ..... Targeted hypoglossal neurostimulation
UAS ..... Upper airway stimulation

Executive Summary

Background: Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that results from a collapse of the upper airway during sleep and may be caused by inadequate muscle tone of the tongue and/or other muscles of the airway. Continuous positive airway pressure (CPAP) is currently the generally accepted standard treatment for moderate-to-severe OSA, but long-term compliance is limited. A potential functional invasive treatment option for patients, not successfully treated with CPAP therapy, is hypoglossal nerve stimulation (HGNS). The technology utilises an implantable device that electrically stimulates the hypoglossal nerve, intended to promote airway patency during the night and improve sleep in OSA patients. Three CE-certified systems are currently available.

obstructive sleep apnea (OSA):

1st line CPAP
new therapy option: hypoglossal nerve stimulation (HGNS)

Methods: Two systematic reviews from 2016 and 2019 have already evaluated the efficacy and safety of HGNS for moderate-to-severe OSA. For the present 2nd update, an update search was performed. Since a EUnetHTA report "Hypoglossal nerve stimulation systems for treatment of obstructive sleep apnea" from 2020 was available, the data of this report were used as a basis and only new studies since the EUnetHTA report were considered for further assessment.

based on EUnetHTA report (2020)
update search

Results: The update search identified three additional trials: one sham-controlled, crossover randomised controlled trial (RCT), one comparative parallel-arm study and one observational registry study (ADHERE registry). For the assessment of efficacy of HGNS compared with no therapy only a single, low quality, comparative, parallel-arm study could be used. In this study the assignment to the intervention group (230 patients) or the control group (100 patients) based on whether or not insurance covered the cost of the implant and patients treated in this study were part of a larger study population (ADHERE registry). Treatment with upper airway stimulation (UAS) compared to no therapy showed significant improvements in sleep-related parameters: Apnea-Hypopnea Index (AHI), Epworth Sleepiness Scale (ESS) and patients' quality of life (Functional Outcomes of Sleep Questionnaire, FOSQ-10) at final visit. The overall usage of UAS was 5.6 h/night.

2nd Update:
3 additional studies identified

efficacy:
1 comparative parallel-arm study (n=330 pts) of low quality

significant improvements

In the RCT, treatment outcomes of patients (n = 86, all with HGNS implantation at least six months prior) were assessed at three time points with weekly intervals. After one week of UAS, patients were randomly assigned in a crossover design to either UAS followed by Sham stimulation (Stim-Sham group, 43 patients) or Sham stimulation followed by UAS (Sham-Stim group, 43 patients). Considering that all patients in the RCT received therapeutic stimulation at baseline and no comparative data are available without UAS, the study was not eligible to evaluate efficacy, but safety only. Therefore, for the assessment of safety of HGNS, this RCT, the parallel-arm study and additional one observational registry study (ADHERE registry) was eligible. None of the three studies reported deaths related to the procedure or the device. However, there were two cardiovascular events reported: a stroke in the RCT and an intraoperative arrest in the single-arm study - both seemingly not device related. Due to the short follow-up of the RCT (two weeks only), no other (serious) adverse events ((S)AEs) were reported. In the observational studies several SAEs (intraoperative and during follow-up) occurred, most of which (73%) were due to serious adverse product-related events (SADEs: sensor lead revision, stimulation lead revision, system revision...). In addition, a large

safety:
3 studies (n=1098 pts): RCT + comparative parallel-arm study + registry-based study

SAE + SADE

AE

number of adverse events (AEs) related to both therapy and device (therapy related discomfort, insomnia/arousal, tongue abrasion…) were recorded across the two observational studies.

available evidence from EUnetHTA report and 2nd Update:

3 comparative studies 8 single-arm studies on pts in ADHERE registry

double (or triple) reporting of pts?

Discussion: Considering the newly identified studies together with the included studies in the EUnetHTA report 2020, a total of three comparative studies are available: one RCT (n = 46, all UAS implanted and responders to UAS) comparing UAS maintenance after 12 months vs. UAS withdrawal after 12 months, one RCT (n = 86) comparing UAS vs. Sham-stimulation in a crossover study with only two weeks follow-up and one parallel-arm study comparing patients with UAS (n = 230) vs. no therapy (n = 100). Additional eight single-arm observational studies are available. The majority of the studies are written by the same authors/ authoring groups and included patients from the same study population (ADHERE registry study): double (or triple) reporting of results cannot be excluded.

no valid conclusion for population of interest possible with available evidence

Conclusion: Based on the three comparative studies no valid conclusion can be drawn about the efficacy of HGNS compared to no therapy in an unselected general population (non-compliant and non-responders to CPAP). Furthermore, the available evidence for safety assessment does not allow conclusions to be drawn about whether HGNS is safe in the population of interest.

Zusammenfassung

Hintergrund: Bei der obstruktiven Schlafapnoe (OSA) handelt es sich um eine schlafbezogene Atmungsstörung, die auf einen Kollaps der oberen Atemwege während des Schlafs zurückzuführen ist und durch einen unzureichenden Muskeltonus der Zunge und/oder anderer Muskeln der Atemwege verursacht werden kann. Kontinuierlicher positiver Atemwegsdruck (CPAP) ist derzeit die allgemein anerkannte Standardbehandlung für mittelschwere bis schwere OSA, aber die langfristige Compliance ist begrenzt. Eine potenzielle funktionelle invasive Behandlungsoption für Patient*innen, die nicht erfolgreich mit CPAP behandelt werden können, ist die Hypoglossusnerv-Stimulation (HGNS). Bei dieser Technologie wird ein implantierbares Gerät verwendet, das den Nervus hypoglossus elektrisch stimuliert, um die Offenheit der Atemwege während der Nacht zu fördern und dadurch den Schlaf von OSA-Patient*innen zu verbessern. Derzeit sind drei CE-zertifizierte Systeme verfügbar.

obstruktive Schlafapnoe (OSA):

1. Wahl CPAP
neue Therapieoption: Hypoglossusnerv-Stimulation (HGNS)

Methoden: Zwei systematische Übersichten aus den Jahren 2016 und 2019 haben bereits die Wirksamkeit und Sicherheit von HGNS bei mittelschwerer bis schwerer OSA evaluiert. Für das vorliegende 2. Update wurde eine Aktualisierungsrecherche durchgeführt. Da ein EUnetHTA-Bericht "Hypoglossal nerve stimulation systems for treatment of obstructive sleep apnea" aus dem Jahr 2020 verfügbar war, wurden die Daten dieses Berichts als Grundlage verwendet und nur neuere Studien seit dem EUnetHTA-Bericht für die weitere Bewertung berücksichtigt.

basierend auf dem EUnetHTA-Bericht (2020)
Aktualisierungsrecherche

Ergebnisse: Bei der Aktualisierungsrecherche wurden drei neue Studien gefunden: eine randomisierte, scheinkontrollierte Crossover-Studie (RCT), eine vergleichende Parallelarmstudie und eine beobachtende Registerstudie (ADHERE-Register). Für die Bewertung der Wirksamkeit von HGNS im Vergleich zu keiner Therapie konnte nur eine vergleichende, parallel-armige Studie von geringer Qualität herangezogen werden. In dieser Studie wurden die Patient*innen abhängig davon, ob die Versicherung die Kosten für das Implantat übernahm oder nicht, entweder der Interventionsgruppe (230 Patient*innen) oder der Kontrollgruppe (100 Patient*innen) zugewiesen. Die in dieser Studie behandelten Patient*innen waren zudem Teil einer größeren Studienpopulation (ADHERE-Register). Durch die Stimulation der oberen Atemwege (UAS) wurden, im Vergleich zu keiner Therapie, zum Zeitpunkt der Abschlussuntersuchung signifikante Verbesserungen bei schlafbezogenen Parametern erzielt: Apnoe-Hypopnoe-Index (AHI), Epworth Sleepiness Scale (ESS) und der Lebensqualität der Patient*innen (Functional Outcomes of Sleep Questionnaire, FOSQ-10). Die Nutzung der UAS betrug insgesamt 5,6 Stunden/Nacht.

2. Aktualisierung: 3 zusätzliche Studien identifiziert

Wirksamkeit: 1 vergleichende, parallel-armige Studie (n=330) Patient*innen

signifikante Verbesserungen

In der RCT wurden die Behandlungsergebnisse der Patient*innen (n = 86, alle mit einer HGNS-Implantation seit mindestens sechs Monaten) zu drei Zeitpunkten in wöchentlichen Abständen bewertet. Nach einer Woche UAS wurden die Patient*innen nach dem Zufallsprinzip in einem Crossover-Design entweder einer UAS mit anschließender Sham-Stimulation (Stim-Sham-Gruppe, 43 Patient*innen) oder einer Sham-Stimulation mit anschließender UAS (Sham-Stim-Gruppe, 43 Patient*innen) zugeteilt. In Anbetracht der Tatsache, dass alle Patient*innen in der RCT zu Beginn eine therapeutische Stimulation erhielten und keine Vergleichsdaten ohne UAS vorliegen, war die Studie nicht zur Bewertung der Wirksamkeit, sondern nur zur Bewertung der

Sicherheit: 3 Studien (n=1098)

SAE + SADE

AE

Sicherheit geeignet. Für die Bewertung der Sicherheit von HGNS waren somit die RCT, die Parallelarmstudie und eine zusätzliche beobachtende Registerstudie (ADHERE-Register) relevant. Keine der drei Studien berichtete über Todesfälle im Zusammenhang mit dem Verfahren oder dem Gerät. Allerdings wurden zwei kardiovaskuläre Ereignisse registriert: ein Schlaganfall in der RCT und ein intraoperativer Herzstillstand in der einarmigen Studie - beide offensichtlich nicht gerätebezogen. Aufgrund der kurzen Nachbeobachtungszeit der RCT (nur zwei Wochen) wurden keine weiteren (schwerwiegenden) unerwünschten Ereignisse ((S)AE) berichtet. In den Beobachtungsstudien traten mehrere SAE (intraoperativ und während der Nachbehandlung) auf, von denen die meisten (73 %) auf schwerwiegende unerwünschte produktbezogene Ereignisse (SADEs: Revision der Sensorleitung, Revision der Stimulierungsleitung, Systemrevision...) zurückzuführen waren. Darüber hinaus wurde in den beiden Beobachtungsstudien eine große Anzahl von unerwünschten Ereignissen (AEs) registriert, die sowohl mit der Therapie als auch mit dem Gerät zusammenhingen (therapiebedingte Unannehmlichkeiten, Schlaflosigkeit/Angst, Abschürfungen der Zunge...).

verfügbare Evidenz aus dem EUnetHTA-Bericht und der 2. Aktualisierung: 3 vergleichende Studien 8 einarmige Studien an Patient*innen im ADHERE-Register

mehrfache Berichterstattung über Pts?

Diskussion: Berücksichtigt man die neu identifizierten Studien zusammen mit den eingeschlossenen Studien im EUnetHTA-Bericht 2020, liegen insgesamt drei vergleichende Studien vor: ein RCT (n = 46, alle UAS implantiert und Responder für UAS) im Vergleich von Weiterbehandlung mit UAS nach 12 Monaten vs. Absetzen von UAS nach 12 Monaten, ein RCT (n = 86) bei dem UAS vs. Sham-Stimulation in einer Crossover-Studie mit nur zwei Wochen Follow-up verglichen wird und eine parallel-armige Studie im Vergleich von Patient*innen mit UAS (n = 230) vs. keine Therapie (n = 100). Zusätzlich sind acht einarmige Beobachtungsstudien verfügbar. Die meisten Studien wurden von denselben Autoren/Autorengruppen verfasst und umfassten Patient*innen aus derselben Studienkohorte (ADHERE-Registerstudie): eine doppelte (oder dreifache) Berichterstattung der Ergebnisse kann nicht ausgeschlossen werden.

keine gültige Schlussfolgerung für die Zielpopulation mit den verfügbaren Daten möglich

Schlussfolgerung: Auf der Grundlage der drei vergleichenden Studien kann keine gültige Schlussfolgerung über die Wirksamkeit von HGNS im Vergleich zu keiner Therapie in einer unselektierten Allgemeinbevölkerung (Patient*innen, die mit CPAP nicht zurechtkommen oder nicht darauf ansprechen) gezogen werden. Darüber hinaus lassen die verfügbaren Evidenzen für die Sicherheitsbewertung keine Schlussfolgerungen zu, ob HGNS in der Zielgruppe sicher ist.

Summary of the EUnetHTA report 2020

EUnetHTA Report 2020

This chapter summarises the results of the EUnetHTA report from 2020 [1] "Hypoglossal nerve stimulation systems for treatment of obstructive sleep apnea".

obstruktive Schlafapnoe

Background: Obstructive sleep apnea (OSA) is a potentially serious sleep disorder in which breathing stops and starts repeatedly during sleep. It results from collapse of the upper airway during sleep and may be caused by inadequate muscle tone of the tongue and/or other muscles of the airway. Underlying anatomic or physiologic factors (e.g. obesity) may increase the susceptibility to collapse. The diagnosis of OSA is generally made by polysomnography (PSG) in a sleep laboratory.

CPAP ist die Therapie der Wahl

HGNS: Patient*innen, die CPAP nicht vertragen

The treatment of choice for moderate-to-severe OSA [Apnea Hypopnea Index (AHI) ≥15] is the Continuous positive airway pressure (CPAP). The clinical use of CPAP can be compromised by poor compliance and some long-term complications, hence patients with inadequate adherence or those who do not respond to CPAP or other non-invasive procedures are of interest for alternative interventions.

Stimulation des Nervus Hypoglossus als Alternativtherapie

One alternative therapeutic approach for such patients is the Hypoglossal Nerve Stimulation (HGNS). Although conventional surgery may be appropriate to correct upper airway obstruction in selected patients, invasive surgical approaches to anatomic restructuring are not relevant comparators to HGNS, because these procedures do not address the underlying pathophysiology of OSA, the inadequate tone of the upper airway musculature.

Implantat zur Neurostimulation

HGNS is a new treatment for OSA that uses neuromodulation via an implantable stimulatory device, resembling a pacemaker, which promotes airway patency throughout the night and thus improves sleep in OSA patients.

3 Produkte auf dem Europäischen Markt

There are three HGNS products available for use in Europe: the Inspire® Upper Airway Stimulation (UAS) System (Inspire Medical Systems, Inc.), the aura6000™ System (ImThera Medical, Inc.) and the Nyxoah's Genio™ system. In addition, there is a product that is no longer available [HNS/HGNS® System* (Apnex Medical, Inc.)].

systematische Literatursuche

Methodology: A systematic literature search in PubMed, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the Cochrane Database for Systematic Reviews, as well as a manual search, was performed according to a predefined search strategy. The search was closed on January 20th 2020 and the final selection for qualitative analysis consisted of eight articles.

1 RCT für die Evaluierung der Wirksamkeit
6 einarmige Beobachtungsstudien zur Evaluierung der Sicherheit

Results: Only one comparative study that sought to assess effectiveness was identified, a randomized controlled therapy withdrawal study on the use of the Inspire® Upper Airway Stimulation System (UAS) (Inspire Medical Systems, Inc.). The authors reported data on effectiveness, but not on safety. Another six studies were selected to assess safety and adherence, all prospective single-arm studies. Those studies examined not only Inspire®, but also the following: the aura6000™ System, Apnex and Nyxoah's Genio™.

The quality of the evidence was very low for both, effectiveness and safety.

RCT nur mit UAS-Respondern

AHI, ESS und FOSQ verschlechterten sich wenn UAS für eine Woche inaktiv

The comparative effectiveness among HGNS devices versus implanted, but deactivated UAS is based on only one small and low-quality randomised controlled study (n=46). This study was conducted with a group of selected patients (all had UAS implanted and were responders in an earlier phase of the trial) and hence not applicable to the entire population of interest. The subjects were randomised to have their device turned ON or OFF during a one-week period. The study showed a significant worsening in AHI, Oxygen desaturation index (ODI), Hypoxemia time (HAT) and quality of life [Epworth sleepiness scale (ESS) and Functional outcomes of sleep questionnaire (FOSQ) scores] when the device was deactivated for one week.

ca 5,7 Stunden pro Nacht in Verwendung

Neither the RCT nor the observational single-arm studies reported any deaths related to the procedure or the device. Although no comparative evidence was found regarding adherence, the largest single-arm study found a median device use of 5.7 hours per night in 382 patients after 12 months of follow-up.

No evidence was found regarding the following crucial outcomes: cardio/cerebrovascular morbidity and long-term effects on quality of life.

RCT liefert keine Daten zur Sicherheit

3,45 % der Patient*innen hatten SAEs

The RCT did not address safety outcomes. Although information from prospective single-arm studies was retrieved and analysed, the quality of evidence regarding safety proved to be very low. A significant number of device- and procedure-related adverse events were reported. An average of 1.02 adverse events per patient was reported: the most frequent non-serious adverse event was discomfort/pain related to the device. 3.45% of patients suffered a serious adverse event. The most frequent serious adverse events were surgical interventions due to replacement, and repositioning or explantation of the device.

Conclusion: As in the RCT only highly selected patients (n = 46) with implants (activated or deactivated) were studied, the available evidence does not allow for any conclusions as to whether HGNS is more effective and safer than no treatment in the general population of interest.

UPDATE 2022

1 Objectives and Scope

1.1 PICO question

PICO-Frage

Is electrical stimulation of the hypoglossal nerve (HGNS) in adult patients with moderate-to-severe obstructive sleep apnea who are not successfully treated with Continuous Positive Airway Pressure (CPAP) therapy more effective and at least as safe in terms of severity of OSA, daytime sleepiness, quality of life, and serious adverse events compared with no intervention?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 1-1.

Table 1-1: Inclusion criteria

Population	Adult patients with moderate-to-severe obstructive sleep apnea, ["Sleep Apnea, Obstructive"] Either not accepting or not adhering to CPAP therapy ["Continuous Positive Airway Pressure"] or have failed conservative treatment ■ ICD-10: G47.3: Sleep apnea, G47.33: Obstructive sleep apnea (adult) ■ MeSH terms: Snoring, Sleep Apnea Syndromes, Electric Stimulation Therapy, Electric Stimulation, Cranial Nerves (Medline and Cochrane)
Intervention	Hypoglossal nerve stimulation (HGNS) ["Electric Stimulation Therapy"]
Control	No stimulation treatment
Outcomes	
Efficacy	Crucial: ■ Severity of obstructive sleep apnea (AHI) ■ Level of daytime sleepiness (ESS) ■ Quality of life (FOSQ) Important: ■ Adherence to treatment
Safety	All events (related or unrelated to the device or intervention): ■ Serious adverse device effect (SADE) ■ Serious adverse events (SAE) ■ Adverse events (AE)
Study design	
Efficacy	Randomised controlled trials (RCTs), prospective non-randomised controlled studies, and other observational comparative studies
Safety	Randomised controlled trials, prospective non-randomised controllesd studies, other observational comparative and non-comparative studies and single arm studies [with at least 10 patients, length of follow-up at least 6 months]

2 Methods

2.1 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 28th of December 2021 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- HTA (INAHTA)

146 Zitate identifiziert seit Nov 2018

3 Studien inkludiert

The systematic search was limited to include articles published between November 2018 and December 2021. The searches in Medline and Embase were limited to (controlled) randomised trials and systematic reviews/ meta-analyses as well as articles published in English or German. Further a non-systematic, manual literature search was conducted on the 11th January 2022. After the removal of duplicates, 146 citations were screened by title and abstract. Finally 3 citations were included. The remaining 20 studies were used for a full-text review, and finally three of them were included for further evaluation. The specific search strategy employed can be found in the Appendix (see Literature search strategies).

By hand-search, no additional citations could be identified.

Suche nach laufenden RCTs in Studienregistern

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 12th of January 2022 that identified three potentially relevant trails (see Appendix Table A - 9).

2.2 Flow chart of study selection

Literaturauswahl 3 Studien für qualitative Synthese eingeschlossen

Overall 146 hits were identified. The references were screened by two independent researchers (VH, CW) and in case of disagreement a third researcher was involved to solve the differences. Due to the fact that an assessment from EUnetHTA on "Hypoglossal nerve stimulation systems for treatment of obstructive sleep apnea" from the year 2020 [1] was available, the decision was made to update this report and to include only new studies for the underlying update since the EUnetHTA report. The selection process is displayed in Figure 2-1.

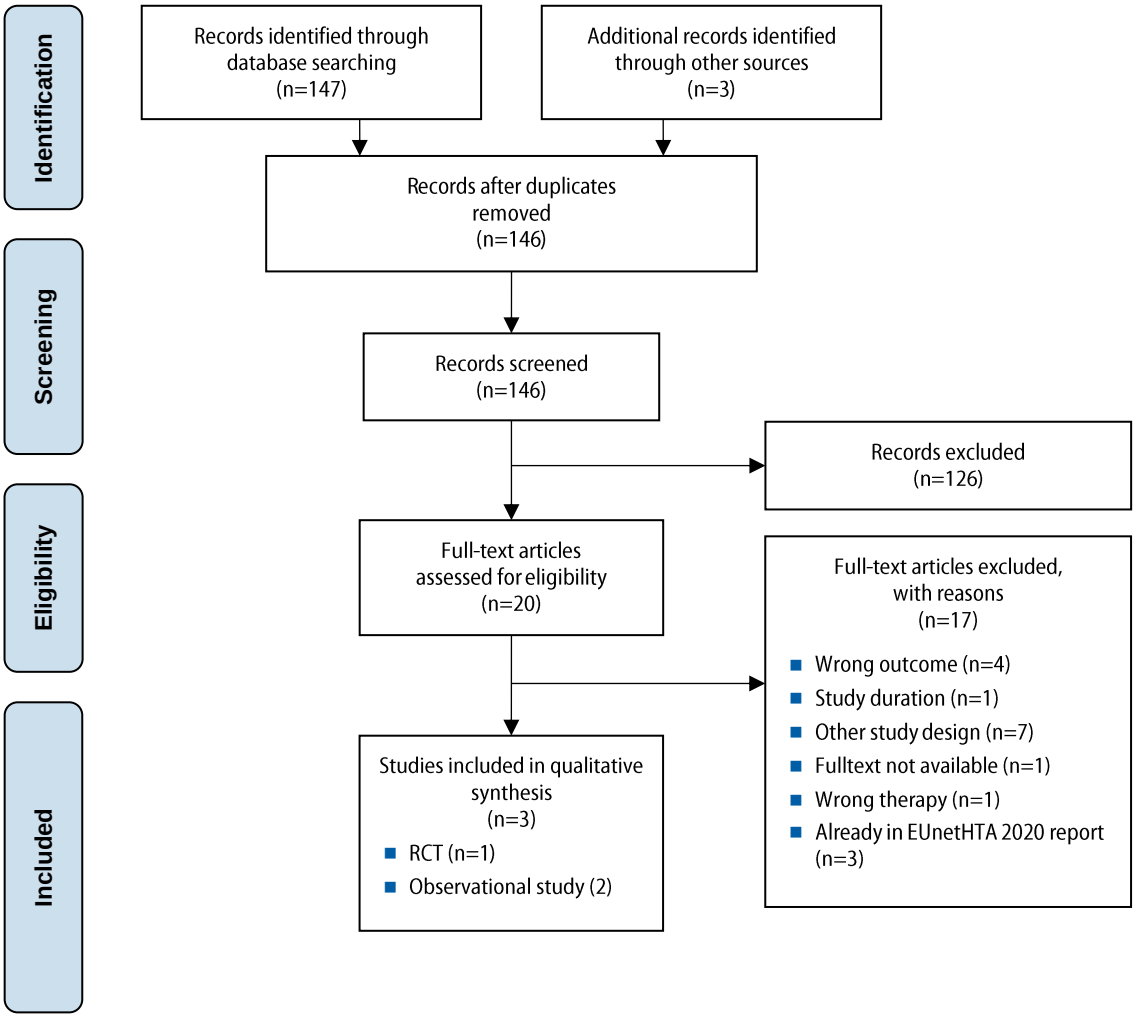

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.3 Analysis and synthesis of the evidence

RoB Assessment

Quality was assessed using the Cochrane Risk of Bias tool 2 [2] for the RCT, the ROBINS-I tool [3] for the comparative nRCT and the "Institute of Health Economics (IHE) RoB checklist" [4] for the observational single-arm study (see Appendix Table A - 6 to Table A - 8).

Extraktion der Daten

One reviewer (VH) systematically extracted relevant data from the included study into data extraction tables. A second reviewer (CW) cross-checked the data extraction tables with the data source and validated them for accuracy. Risk of bias was conducted by independent researchers (VH, CW) and differences were settled via consensus.

Bewertung der Qualität der Evidenz mit GRADE

Two reviewer analysed the quality of the data using GRADE [5] (CW, VH). Based on the data extraction tables (see Appendix, Table A - 3, Table A - 4, Table A - 5), data on each selected outcome category were, if applicable, synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [6]. The research questions were answered in plain text format with reference to GRADE evidence tables (Table 4-1).

3 Results: Clinical effectiveness and Safety

3.1 Outcomes

3.1.1 Outcomes effectiveness

wesentliche Endpunkte für Wirksamkeit:

For the evaluation of effectiveness the following outcomes were defined as crucial to derive a recommendation:

- Severity of obstructive sleep apnea (AHI)
- Level of daytime sleepiness (ESS)
- Quality of life (FOSQ)

Schwere der OSA
Tagesschläfrigkeit
Lebensqualität

Apnea-Hypopnea Index (AHI): Indikator für Schwere der Schlafapnoe

The **Apnea-Hypopnea Index (AHI)** is an index used to indicate the severity of sleep apnea. It is represented by the number of apnea and hypopnea events per hour of sleep. AHI is one of several sleep study measures in polysomnography, but it is not a clinical or health outcome. In adults, an AHI less than 5 events per hour is considered normal. Mild OSA is defined as an AHI between 5 and 15 events per hour, moderate OSA between 15 and 30 events per hour, and severe OSA as greater than 30 events per hour [7]. In studies, the reduction of more than 50% and less than 20 has been defined as a clinically meaningful improvement of AHI.

AHI unabhängiger Prädiktor für Mortalität

There were two studies addressing health outcomes like cardiovascular morbidity but no data was reported on cardiovascular mortality. However, AHI greater than 30 events per hour is an independent predictor of all-cause mortality, but the evidence is insufficient regarding the association between AHI and other clinical outcomes [8].

Epworth Sleepiness Scale (ESS): validiertes Messinstrument für Tagesschläfrigkeit

The **Epworth Sleepiness Scale (ESS)** [9] is a validated subjective measure of sleep propensity. The ESS differentiates between average sleepiness and excessive daytime sleepiness and focuses solely on sleepiness and no other signs and symptoms of OSA. The ESS asks people to rate their usual chances of dozing off or falling asleep in 8 different situations or activities that most people engage in as part of their daily lives, although not necessarily every day. Based on a study of normal subjects, the reference range is defined as ≤10 [10, 11]. Data show that "normal" adults who do not have evidence of a chronic sleep disorder (including snoring) have a mean ESS score of 4.6 (95% CI 9-5.3) with a SD of 2.8 [12]. A higher score indicates an increased risk to fall asleep during daily activities. 1 point change in ESS is considered to be clinically significant.

krankheitsspezifische Lebensqualität: FOSQ Fragebogen

The **Functional Outcomes of Sleep Questionnaire (FOSQ)**, a disease specific quality-of-life measure, assesses the impact of disorders of excessive sleepiness (DOES) on functional outcomes relevant to daily behaviours and quality of life. The potential range of scores for the total score is 5-20, where a higher score implies better subjective sleep quality. 2.0 points increase is considered a minimally important difference.

wichtig aber nicht entscheidend: Therapietreue

Further outcomes defined as important, but not crucial to derive a recommendation, include the **adherence to treatment**. The assessment of adherence is necessary for effective and efficient treatment planning and is intended to ensure that changes in health status can be attributed to the treatment program under investigation. However, there is no "gold standard" for measuring adherence behavior, which requires adjustment according to the particular drug/intervention [13]. For OSA, the main measurement is the usage of HGNS.

3.1.2 Outcomes safety

wesentliche Endpunkte für Sicherheit:

(schwere) unerwünschte Nebenwirkungen (S)AE

schwere produktbezogene unerwünschte Effekte (SADE)

For the evaluation of safety the following outcomes were defined as crucial to derive a recommendation:

- Adverse Events (AE)
- Serious Adverse Events (SAE) and
- Serious Adverse Device Effects (SADE)

In accordance with the guidelines of medical devices on serious adverse event reporting, these outcomes have been selected.[1]

Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational device or related to the procedures involved (any procedure in the clinical investigation plan).

Serious Adverse Event (SAE) is an adverse event that led to a death, to a serious deterioration in health of the subject that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function. Alternatively, an event that led to in-patient hospitalisation or prolongation of existing hospitalisation, or medical or surgical intervention to prevent life threatening illness or injury.

Serious Adverse Device Effect (SADE) is an adverse event related to the use of an investigational medical device that has resulted in any of the consequences characteristic of a serious adverse event. First, this includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device. Second, this includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

[1] https://ec.europa.eu/health/system/files/2020-09/md_mdcg_2020-10-1_guidance_safety_reporting_en_0.pdf

3.2 Included studies

1 RCT
2 prospektive Beobachtungsstudien:
1 parallel-arm Studie
1 prospektive Registerstudie

Additional to earlier clinical trials identified in 2016 (“Upper Airway Stimulation for Moderate-to-Severe Sleep Apnea”) [14], the 1. Update 2019 (“Implantation eines Systems zur Stimulation des Nervus Hypoglossus bei obstruktiver Schlafapnoe”) [15] and the EUnetHTA report 2020 ("Hypoglossal nerve stimulation systems for treatment of obstructive sleep apnea") [1], the literature search identified two prospective comparative studies (one multicentre, double-blinded, randomised, sham-controlled, crossover study [16] and one parallel-arm study [17]), though only [17] could be used on efficacy outcomes: Considering that all patients in the RCT [16] received therapeutic stimulation at baseline and no comparative data are available without UAS, only the comparative parallel-arm study [17] was eligible to assess efficacy.

For the assessment on safety, besides the two studies mentioned above, an observational single-arm registry study could be used [18] (see Table A - 3 to Table A - 5).

3.2.1 Study characteristics

RCT: Stim-Sham Gruppe (45 Pts) vs. Sham-Stim Gruppe (44 Pts)

vergleichende parallel-arm Studie: 250 Pts mit UAS vs. 100 Pts ohne Therapie

einarmige Beobachtungsstudie: 1.786 Pts mit UAS-Implantat
Industrie gesponsert

variable Nachbeobachtungszeit
FU: 2 Wochen - 14 Monate

3-945 Pts nicht weiterbeobachtet

The RCT [16] enrolled 89 patients who were randomly assigned to either UAS followed by Sham stimulation (Stim[2]-Sham[3] group, 45 patients) or Sham stimulation followed by UAS (Sham-Stim group, 44 patients) after 1 week of UAS therapy. The comparative observational study [17] included 250 subjects with a UAS implant for comparison with 100 subjects without an implant ("no therapy"), with group allocation based on whether or not insurance covered the cost of implantation. The single-arm observational study [18] included 1849 patients, of whom 1786 had an implant at the time of analysis. Of these, a total of 1019 patients reached the one to two year follow-up period, with outcome data collected from 782 of these patients. In addition, a subanalysis for two BMI groups (BMI_{32} vs BMI_{35}) was performed in the study just mentioned. Overall, 2107 patients with an HGNS implant were included in the three multicentre studies ([16] conducted in Germany and [17, 18] in both Germany and the United States). All studies (and the registry) were written by authors with CoI and sponsored by Inspire Medical.

The follow-up time of the RCT was two weeks and three patients were excluded from the final analyses. For the parallel observational study, the median follow-up time was one year (358 days), whereas the follow-up time in the comparison group ("no therapy") was significantly shorter (175 days). In the single-arm observational study, the last visit was 14 months after implantation. The number of patients who withdrew from the nRCTs ranged from 30 to 945 subjects.

The RCT and nRCTs assessed the following important endpoints: apnoe hypopnea index (AHI), Epworth sleepiness scale (ESS), functional outcomes of

[2] STIM = continued therapeutic stimulation, average amplitude 1.6 V ± 0.7

[3] SHAM = stimulation voltage set at 0.1 V as a subtherapeutic stimulation level and a deception for the patient

sleep questionnaire (FOSQ), use of UAS as well as adverse events (AE) and serious adverse events (SAE).

Verzerrungsrisiko der eingeschlossenen Studien: moderat bis hoch

The risk of bias for the RCT was considered high, mainly due to the lack of published data before therapy initiation and at the individual measurement time points. The risk of bias for the parallel-arm study was rated as serious, with major concerns related to the large amount of losses to follow-up in both groups, the different measurement methods used at the various study sites, and the fact that the intervention group was part of a larger study cohort (ADHERE registry), which may lead to selectively reported data. The overall risk of bias for the registry study was considered to be moderate mainly due to the high number of losses to follow-up in both groups, leading to missing outcome data at the final visit.

3.2.2 Patients characteristics

Einschlusskriterien: Pts ≥18 Jahre, moderate bis schwerwiegende OSA, kein vollständiger konzentrischer Kollaps während DISE

The studies' inclusion criteria for the patients were quite similar: patients ≥18 years of age, with moderate-to-severe OSA (AHI ≥15), intolerance to continuous positive airway pressure (CPAP), and absence of complete concentric collapse during drug-induced endoscopy (DISE). In addition, the RCT included only patients who had a UAS implant for at least six months, and patients were excluded if they were unwilling to undergo three PSGs in the laboratory within one month or if the physician considered them unsuitable for participation. The latter, as well as patients with more than 25% central and mixed apneas and a life expectancy <1 year, were exclusion criteria in the nRCTs.

Mehrheit männlich

In the RCTs, most patients were male (81%) and of Caucasian origin (100%) with a mean age of 57.5 years and BMI of 29 kg/m^2. A similar pattern was observed in the observational studies (in both studies, patients treated with UAS were part of the ADHERE registry): 70-84% of patients were male and of Caucasian origin (95-99%) with a mean age of 57.5 to 60 years and BMI of 29 to 30 kg/m2.

Study characteristics and results of included studies are displayed in *Table A* - 1 and Table A - 2, the risk of bias (RoB) assessment in Table A - 6 to Table A - 8.

3.3 Results

3.3.1 Resuts: effectiveness

1 vergleichende Beobachtungsstudie für Bewertung der Wirksamkeit Ergebnisse zu 330 Pts

For effectiveness, data of one comparative trial with 250 UAS patients (but with data presented on primary endpoints only for 230 patients) vs. 100 patients with no therapy and a follow-up time between the groups of 356 days vs. 175 days could be used [17].

Severity of obstructive sleep apnea (AHI)

At the final follow-up, the AHI reduction from baseline [I (n = 228): -19.1 ± 15.8 vs. C (n = 100): -8.1 ± 20.9, p<0.001] was significantly larger in the intervention group compared with the control group [I (n = 228): 14.7 ± 13.8 vs. C (n = 100) 26.8 ± 17.6, p<0.001].

signifikante Veränderungen bei AHI

Level of daytime sleepiness (ESS)

The ESS score showed significant improvement from baseline to follow-up [I (n = 222): -5.1 ± 5.5 vs. C (75): 1.8 ± 3.7, p<0.001] in the therapy group compared with the control group at final visit [I (n = 226): 7.2 ± 4.8 vs. C (n = 90): 12.8 ± 5.2, p<0.001].

signifikante Verbesserung bei ESS

Quality of life (FOSQ)

The quality of life measured by the FOSQ-10 was higher in the intervention group (n = 221) compared with the control group (n = 75) (17.1 ± 3.2 vs. 12.4 ± 3.7, p<0.001) at final visit.

signifikante Verbesserung bei FOSQ-10

Adherence to treatment

Objective therapy use was downloaded from the UAS device and showed an average UAS use in the intervention group of 5.6 ± 2.0 hours/night. 92% of participants used UAS more than 20 hours per week and 77% of patients used the therapy more than 28 hours.

durchschnittliche Therapienutzung von 5,6 h/Nacht

3.3.2 Resuts: safety

For the assessment of the safety of HGNS, the RCT (n = 86) [16] and the observational registry study [18] (n = 1768) were used in addition to the parallel-arm study (n=330) [17]. The follow-up period in the newly included studies ranged from 2 weeks to one year.

1 RCT, 2 Beobachtungsstudien für Bewertung der Sicherheit

Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADE)

Overall, two cardiovascular events were reported: in the RCT [16], one subject suffered a stroke while the stimulation was switched on (this could not be assigned to the therapy) and in the observational registry study [18], one patient suffered an intraoperative (anaesthesia-dependent) arrest. In this study [18], additional seven intraoperative SAEs were reported in 1849 patients (0.43% of patients) and it was observed that surgical success was less likely in patients with BMI ≤35 kg/m^2 compared to BMI ≤32 kg/m^2 (72.2% vs. 59.8%, p<0.02). Further 35 SAEs occurred during the follow-up. In the parallel-arm study [17] one SAE was reported in one patient, requiring two surgical procedures to reposition the uncomfortable position of the stimulation lead (4.5 % of total severity (AE plus SAE)).

1 SAE in RCT und 44 SAEs in Beobachtungsstudien, davon 73 % SADEs

Overall one SAE was observed in the RCT and 44 SAEs were reported [16-18] in the observational studies, whereas the majority (73 %) were related to device e.g. surgical reposition, system, sensor or stimulation lead revision.

SADE: chirurgische Repositionierung oder Revision

Adverse Events (AE)

AE: 3-45% Pts in 2 Studien berichtet

AE: Unbehagen, Schlaflosigkeit, Zungenabrieb und -irritation

In the parallel-arm study [17] 3 % of patients suffered operative complications which were rated as mild (71%) or moderate (29%) and 5% of patients had therapy-related complications classified as mild or moderate in severity. In the observational registry study [18] a total of 349 patients (45 % of 782 pts with follow up data) reported non-serious adverse events during the follow-up period, whereas the most common events were stimulation-related discomfort (in 151 pts), insomnia/arousals and tongue abrasion/irritation.

4 Quality of evidence

Verzerrungsrisiko: 2 Studien hohes Risiko, 1 Studie moderates Risiko

ROB for individual studies was assessed with the Cochrane Risk of Bias 2 tool for the RCT [2], the Robins-I tool [3] for the parallel-arm study and the IHE-Checklist [4] for the single arm observational study and is presented in Table A - 6 to Table A - 8 in the Appendix. The risk of bias is classified as high in the RCT, as serious in the parallel-arm study and as moderate in the single arm observational study.

The strength of evidence was rated according to GRADE [6] for each endpoint individually. Each study was rated by two independent researchers (CW, VH). All disagreements were resolved among the researchers. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [6].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

According to the GRADE scheme for the research question, the ranking can be found in the evidence profile below (Table 4-1).

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile (RoB) in Appendix in Table A - 6 to A-8.

Overall the strength of evidence for the effectiveness and safety of Hypoglossal nerve stimulation (HGNS) in comparison to no treatment is very low.

Table 4-1: GRADE evidence profile for efficacy and safety of Hypoglossal Nerve Stimulation (HGNS)

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	I (n pts)	C (n pts)	Mean ± SD/ n of events		
Effectiveness (parallel-arm, observational study evidence)											
Severity of obstructive sleep apnea **(follow-up: IG: 358 vs. C: 175, assessed with: apnoe hypopnoe index (AHI); higher value indicates a higher severity of OAS)**											
1	Parallel-arm observational study	serious[4]	not serious	serious[5]	serious[6]	none	228	100	14.7 ± 13.8 vs. 26.8 ± 17.6 p<0.001	⊕◯◯◯ Very low	CRUCIAL
Level of daytime sleepiness **(follow-up: mean C: 358 vs.C: 175, assessed with: Epworth sleepiness scale (ESS); higher score indicates an increased risk to fall asleep during daily activities)**											
1	Parallel-arm observational study	serious[4]	not serious	serious[5]	serious[6]	none	226	90	7.2 ± 4.8 vs. 12.8 ±5.2 p<0.001	⊕◯◯◯ Very low	CRUCIAL
Quality of life (follow-up: mean C: 358 vs.C: 175, assessed with: functional outcomes of sleep questionnaire (FOSQ);higher score indicates better subjective sleep quality)											
1	Parallel-arm observational study	serious[4]	not serious	serious[5]	serious[6]	none	221	75	17.1 ± 3.2 vs. 12.4 ± 3.7 p<0.001	⊕◯◯◯ Very low	CRUCIAL
Safety (RCT evidence)											
Serious adverse events (SAE) and Serious Adverse Device Effects (SADE) (follow-up: 2 weeks)											
1	Crossover RCT	serious[7]	not serious	not serious	serious[8]	none	86	86	1 stroke during stimulation	⊕⊕◯◯ Low	CRUCIAL
Adverse events (AE) (follow-up: 2 weeks)											
1	Crossover RCT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Safety (nRCT evidence)											
Serious adverse events (SAE) and Serious Adverse Device Effects (SADE) (follow-up: 1 year)											

[4] large differences between study sites in some variables, missing data on outcomes at final visit, different measurement methods across the countries and before and after intervention, assessors and patients were aware of the intervention

[5] at least one of the cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis oft he results

[6] large standard deviations (SD), studies with small numbers of participants and high loss to follow up

[7] missing data on outcomes at final visit, short study duration

[8] no CI, studies with small numbers of participants and/or high loss to follow up

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	I (n pts)	C (n pts)	Mean ± SD/ n of events		
2	1 Parallel-arm (PA) observational study, 1 single arm (SA) registry study)	serious[4,9]	Not serious	serious[5]	serious[8]	none	2018	100	All SAE in I: SA: 1 intraoperative cardiovascular event, 7 other intraoperative SAEs, 35 SAEs during FU PA: one SAE due to two surgical revisions to reposition an uncomfortable stimulation lead position most SAE were attributable to SADE (73%)	⊕◯◯◯ Very low	CRUCIAL
Adverse events (AE) (follow-up: 1 year)											
2	1 Parallel-arm (PA) observational study, 1 single arm (SA) registry study)	serious[4,9]	not serious	serious[5]	serious[8]	none	2018	100	all AE in I: PA: 3 % pts operative complications: 71% mild and 29% moderate; 5% pts. therapy-related complications (mild or moderate) SA registry: 45 % pts non-serious adverse events, in FU: stimulation-related discomfort, insomnia/ arousals and tongue abrasion/ irritation. 3-35 % of patients with AE	⊕◯◯◯ Very low	CRUCIAL

Abbreviations: *AE = Adverse Event; AHI = Apnoe-Hypopnoe-Index; C = Comparator group; CI = Confidence Interval; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; FU = Follow-up; HGNS = Hypoglossal Nerve Stimulation; I = Intervention group; NA = Not applicable; n = Number; n.r. = not reported; PA = Parallel-arm; pts = Patients; SA = Single-arm; SADE = Serious Adverse Device Effect; SAE = Serious Adverse Event; SD = Standard Deviation*

[9] PA study: serious risk of bias, observational SA study: moderate risk of bias

5 Discussion

Obstructive sleep apnea (OSA) is caused by repetitive obstruction of the upper airway during sleep, resulting in hypopnea or apnea with intermittent hypoxia and transient arousals. Upper airway collapse during sleep is caused by an inadequate motor tone of the tongue and/or other muscles of the airway. Physical factors, such as obesity, can also increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues. Untreated OSA can lead to reduced quality of life, daytime sleepiness, reduced daily activity and consequently favour secondary diseases such as cardiovascular diseases, cognitive impairments and increase the risk of involvement in work and traffic accidents [19]. Continuous positive airway pressure (CPAP) is currently the generally accepted standard treatment for moderate-to-severe OSA [20]. CPAP proved to be effective in both improving quality of life and reducing cardiovascular disease [21], but long-term compliance is limited [22, 23]. Alternative treatments for such patients include invasive procedures like surgery on soft palate or the base of tongue. These invasive procedures can be associated with severe side effects [24, 25] and do not completely address the underlying pathophysiology of OSA, the inadequate tone of the upper airway musculature. An alternative invasive therapeutic approach is hypoglossal nerve stimulation (HGNS), which uses neuromodulation via an implantable device to promote airway patency during the night.

obstruktive Schlafapnoe: schlafbezogene Atmungsstörung durch Kollaps der Rachenmuskulatur

CPAP ist Standardtherapie, aber Compliance ist gering

alternative invasive Therapien

The aim of this 2nd update [14, 15] was to re-assess the efficacy and safety of hypoglossal nerve stimulation in the treatment of moderate-to-severe obstructive sleep apnea compared with no treatment using new available evidence since the EUnetHTA report 2020 [1].

Ziel war, neue Evidenz zu Wirksamkeit und Sicherheit von HGNS zu finden und zu bewerten

Summary of findings (2.Update)

The systematic literature search identified three new studies: one randomised controlled trial (RCT) [16], one parallel-arm study [16, 17] and one single-arm observational registry study [18]. All identified studies were funded by industry and conducted by authors with declared conflicts of interest (CoI). Overall 2107 patients with an Inspire Medical Systems implant were enrolled in the three studies. The inclusion criteria of the study were quite similar: patients ≥18 years, with moderate-to-severe OSA (apnea hypopnea index (AHI) ≥15), intolerance to CPAP, and absence of complete concentric collapse during drug-induced endoscopy (DISE). Additionally, in the observational studies patients with more than 25% of central and mixed apneas were excluded.

1 RCT +
2 Beobachtungsstudien mit 2.107

The only relevant comparative study to evaluate the efficacy of HGNS is a parallel-arm study comparing 250 patients with an upper airway stimulation (UAS) implant vs. 100 patients without an implant ("no therapy") [17]. The parallel-arm study showed a statistically significant improvement in the apnea hypopnea index (AHI), on the Epworth sleepiness scale (ESS) and in the functional outcomes of sleep questionnaire (FOSQ) in the patients with UAS therapy compared with baseline measurements and the control group after one year. The overall average usage of UAS was 5.6 h/night. The study was evaluated to have serious risks of bias.

für Wirksamkeit
1 Beobachtungsstudie mit Vergleich von UAS vs. keine Therapie (n=350)

sign. Verbesserung von AHI, ESS und FOSQ

For the safety assessment the reported outcomes of one RCT [16], one parallel-arm study [17] and one observational registry study [18] could be used with

für Sicherheit:
alle 3 Studien
RCT: nur 2 Wochen FU
parallel-arm Studie: 6-12 Monaten FU
Registerstudie: 14,3±7 Monate FU

very short follow-up (RCT [16]) and mid-term follow-up of 6-14,3 months in the observational studies [17, 18].

2 kardiovaskuläre Ereignisse

1 SAE in RCT und 44 SAEs in nRCTs (davon 73 % SADEs)

viele AE: 3-45% der Pts

No deaths were reported in any of the studies but two cardiovascular events were documented: one stroke in the RCT [16] and one intraoperative arrest in the single-arm observational study [18], both not attributable to the implant. The mentioned observational study [18] reported overall 43 serious adverse events (SAEs) (in 2.3% of patients) and one SAE was documented in the parallel-arm study [17]. About 73 % of the reported SAEs in the nRCTs could be attributed to serious adverse device-related events (SADE). Adverse events (AEs, mild and moderate) such as pain, tongue abrasion and temporarily limited tongue mobility were frequently reported (in 3-45 % of patients), both device- and procedure-related.

Interpretation of the findings

gesamte Evidenz (inkl. EUnetHTA 2020 Bericht):

3 vergleichende Studien und 8 einarmige Beobachtungsstudien

Considering the newly identified studies together with the included studies in the EUnetHTA report 2020 [1], a total of three comparative studies, using the UAS Inspire Medical System, are available: one RCT (n = 46) comparing UAS maintenance after 12 months vs. UAS withdrawal after 12 months [26], one RCT (n = 86) comparing of which UAS vs. Sham-stimulation in a cross-over study with only two weeks [16] and one parallel-arm study comparing patients with UAS (n = 250) vs. no therapy (n = 100) [17].

selbe Autorengruppen Patient*innen aus ADHERE

mehrfach Auswertung von Patient*innen-Daten sehr wahrscheinlich

Additional eight single-arm observational studies (Kezirian et al, 2014 (n = 31, 8 sites: USA and Australia) [27], Woodson et al., 2018 (n = 126, 22 sites: USA, Europe) [28], Eastwood et al., 2020 (n = 27, 7 sites: Australia, France, UK) [29], Steffen et al. 2019 (n = 60, 3 sites: Germany) [30], Hofauer et al., 2019 (n = 102, 2 sites: Germany) [31], Thaler et al., 2019 (n = 640, 6 months; n = 382, 12 months, multicentre USA and Europe) [32] as well as Suurna et al., 2021 (n = 1019, 1 year; 823 final follow up, 43 global centres) [18] evaluating the UAS Inspire Medical System and Friedman et al., 2016 (n = 46, 7 sites: USA, Germany, Belgium) [33] evaluating the THN of ImThera aura6000 system) are available.
The majority of the studies are written by the same autors/ authoring groups and included patients from the same study population (ADHERE registry study): double (or triple) reporting of results cannot be excluded.

1 RCT mit schlechter Qualität und kleiner Studienpopulaton

nur Responder wurden randomisiert = Verzerrung des Bildes zugunsten (guter) Ergebnisse

A comparative “withdrawl of active therapy” study was conducted as RCT by Woodson et al., 2014 [26]: in this small (46 pts) study of low-quality all patients received UAS implants (in an earlier phase of the trial) and only responders were randomised to UAS maintenance after 12 months vs. UAS withdrawal after 12 months. It therefore should be noted that the observed significant treatment effects for AHI, ESS and FOSQ in this study [26] may have been more pronounced than they would have been in an unselected population, as randomised withdrawal trials are enriched with responders and individuals who do not tolerate treatment are excluded [34]. Furthermore, it was not possible to draw any conclusions about the safety of HGNS, since no SAEs and AEs were addressed.

In the newly identified RCT [16] by Heiser et al. 2021, all patients (89 pts) received therapeutic stimulation at baseline and were then randomly assigned in a crossover design to either UAS followed by Sham stimulation (Stim-Sham group, 45 patients) or Sham stimulation followed by UAS (Sham-Stim group, 44 patients) and observed for only 2 weeks. A total of 76.6% patients were effectively treated, according to study investigators and 73.3% with Stim therapy turned out to be AHI responders. However, also 29.5% of the Sham group turned out to be AHI responders, although they had not received any therapeutic stimulation, showing a large placebo-effect. Since there are no comparative data without any UAS available, the reported significant effects in AHI, ESS and FOSQ are only valid to draw conclusions on the placebo effect under sham treatment. Therefore, the study is not appropriate for the evaluation of the efficacy of HGNS compared with no therapy. This study also provided little data in the evaluation for safety. Due to the short follow-up time, no (S)AEs besides a stroke (deemed unrelated to the device) could be observed; moreover, no data on AEs from the period between implantation and randomisation were available.

1 RCT mit fehlenden Daten zu keiner UAS-Therapie, nur 2 Wochen FU (und keine SAE/ AE Informationen)

großer Placebo-Effekt von 29,5%

In the multicentre parallel arm study by Mehra et al., 2020 [17] 250 patients with UAS (of which only for 230 primary outcome data was available) were compared with a cohort of 100 patients without treatment. The effects of this non-randomised study are statistically significant; however, many patients in both groups were "lost-to-follow-up" and there are some safety concerns: about 10% reported treatment-related AE and 3.4% reported postoperative AE. In addition, the study has a high risk of bias; follow-up differed between the two groups, and in some cases, different measurement methods were used at different study sites.

1 nRCT mit Vergleich von UAS vs. keine Therapie

Ergebnisse kritisch betrachten

The observational studies report many adverse events [18, 27-30, 32, 33] related to both device and therapy. The majority of SAEs were due to revision surgery of the implant, and the most commonly cited non-serious AEs included discomfort from the implant, tongue abrasion, and temporary tongue weakness.

viele AE (und SAE), die meisten SADE

Based on the 3 comparative studies, no valid conclusion can be made about the effectiveness of HGNS compared to no therapy in an unselected general population (non-compliant and non-responders to CPAP). In addition, the available evidence for the safety assessment does not allow for any conclusions as to whether HGNS is safe in the population of interest.

Studien geben keine valide Aussage zur Wirksamkeit und Sicherheit

Two additionally identified meta-analyses by Kompelli et al., 2019 [35] (based on case series) and Constantino et al., 2020 [36] (based on prospective single-arm cohort studies) showed an improvement in sleep-related outcomes as well as in quality of life. However, it is also stated that certain groups have a greater benefit from the therapy [35], e.g. patients with a BMI $\leq$35 kg/m^2. This effect has also been shown in therapy usage and surgical success in the observational study by Suurna et al., 2021 [18]. Regarding safety, several patients experienced non-severe adverse events, e.g., tongue abrasion, discomfort due to electrical stimulation [35, 36] and some patients required surgical repositioning or replacement of the neurostimulator or implanted leads within 5 years [36]. Since no RCTs were included in the analyses, the evidence of these analyses is to be rated low. A retrospective analysis comparing various outcome variables of patients from the ADHERE registry with an international multicentre cohort with similar CPAP intolerant OAS patients, receiving traditional surgery for the treatment of OAS, showed positive effects on efficacy regarding

2 Meta-Analysen basierend auf heterogenen Studien zeigen positive Effekte von UAS

1 retrospektive Analyse zeigt ebenfalls positive Effekte, aber unter Limitationen

UAS [37]. However, it should be mentioned that the study has some limitations in the ability to compare the groups (e.g. for AHI) and baseline demographics as well as the follow-up times between the groups differed.

Europäische Leitlinien:

NICE/ UK: nur in klinischen Studien

Fachgesellschaften in DE (S3 Leitlinie) + CH: nur in ausgewählten Pts

A NICE Report 2017 [38] on hypoglossal nerve stimulation for moderate-to-severe obstructive sleep apnea states: "Current evidence on the safety and efficacy of hypoglossal nerve stimulation for moderate-to-severe obstructive sleep apnoea is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research." According to the German S3-Leitlinie "Atmungsstörungen bei Erwachsenen" (recommendation grade B) [39] and the "Empfehlungen der "Swiss Society for Sleep Research, Sleep Medicine and Chronobiology" (SSSSC) zu Diagnose und Therapie der Schlafapnoe"[40], HGNS can be used as an alternative therapy for moderate-to-severe OSA in "certain" individuals with CPAP intolerance.

Evidence gaps and ongoing studies

3 laufende RCTs: Fertigstellung 2023, aber wenig relevant

Three ongoing RCTs were identified with estimated completion dates within the next two years. Of which one study compares a one-month intervention with UAS against a control group with no intervention after one month. More detailed information is listed in Table A - 9 in the Appendix.

fehlende Evidenzen aus RCTs auch in Zukunft

Currently, no relevant RCTs comparing UAS with no therapy over a longer time period and larger study population are available, so the evidence for the assessment of safety and efficacy will stay low. Furthermore, the study populations are mainly male and of Caucasian origin, making them not generalizable to women or non-Caucasians.

Internal and external validity

For the assessment, no RCTs could be used to evaluate effectiveness and for the analysis of safety the RCT does not provide sufficient evidence due to the short duration of the study. For this reason, the evidence on efficacy and safety is primarily from observational studies. Furthermore, the identified RCT and parallel-arm study were rated with a high risk of bias.

verfügbare Evidenz auf Österreich übertragbar

The studies can be perceived as valid also to the Austrian context due to the study population and the study locations.

Limitations

Limitationen: nur prospektive Studien, Aufbau auf EUnetHTA Bericht

Limitations of this 2nd Update are that only prospective studies were considered and that the systematic review and the data extraction from the EUnetHTA report 2020 was mostly adopted (without further processing).

Conclusion

Schlussfolgerung:

keine ausreichende Evidenz

Based on the newly identified studies and the results from the EUnetHTA report, the overall strength of evidence for the efficacy and safety of hypoglossal nerve stimulation (HGNS) compared with no treatment is considered to be low. There is a lack of unbiased information on the durability of the device and long-term data on treatment effects, complications and/or compliance in a general population that could be obtained through a longer follow-up are not available. Furthermore, there is a need for well-conducted RCTs with a longer study duration and comparative data of HGNS vs. no therapy

6 Recommendation

In Table 6-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 6-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

keine ausreichende Evidenz

The current evidence is not sufficient to prove, that the assessed technology hypoglossal nerve stimulation (HGNS) for treating moderate-to-severe obstructive sleep apea is more effective and equally safe than no treatment in the patient population of interest.

The re-evaluation is recommended in 2024.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A - 1: Study characteristics of randomized controlled trials (RCTs)

Study reference/ID (NCT) Author year	Sites or regions, countries, time of study	Study type	Intervention [number of (randomized / enrolled) patients] Name device	Comparator(s) [number of (randomized / enrolled) patients] Name device	Patient population Clinical stage	Endpoints Length of Follow-up
NCT01161420 Woodson et al., 2014 [26]	Belgium 1 site France 2 sites Germany 3 sites The Netherlands 1 site USA 15 sites 2010 - 2017 Nov 2010 - Feb 2012 (recruitment)	Randomised controlled (with only UAS responders) withdrawal study based on observational cohort study [126 patients] Strollo et al. 2014 [41]	UAS [23/46 patients] Inspire Medical Systems, Inc., Maple Grove, Minnesota	Until 13-months UAS was performed, then UAS OFF for 1 week (therapy withdrawal) [23/46 patients] Inspire Medical Systems, Inc., Maple Grove, Minnesota	Moderate-to-severe OSA Intolerance or inadequate adherence to CPAP Exclusion criteria: BMI >32 kg/m^2	ESS, FOSQ, Intrusive snoring, as reported by participant and bed partner Sleep-disordered breathing Follow-up: 12 months + 1 week and 18 months
NCT03760328 Heiser et al., 2021 [16]	Germany 3 sites 2019 - 2020	Multicentre, double-blinded, randomized study (with cross-over design)	Stim-Sham-Stimulation[10] [45/89 patients] Inspire Medical Systems, Dolden Valley, MN, USA	Sham-Stim-Stimulation [44/89 patients] Inspire Medical Systems, Dolden Valley, MN, USA	≥18 years old moderate-to-severe OSA (AHI ≥15), CPAP intolerance, Absence of complete concentric retroplatal collapse during DISE Exclusion criteria: Unwilling to complete three in-lab PSGs within a 1-month timeframe Investigator deems subject is unfit for participation	AHI responders: AHI <15/h ESS, FOSQ, PSS, CGI-I Follow-up: 2 weeks

Abbreviations: *AHI = Apnea Hypopnea Index; BMI = Body Mass Index; CGI-I = Clinical Global Impression of Improvement; CPAP = Continuous positive airway pressure; DISE = Drug-Induced Sleep Endoscopy, ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; OSA = Obstructive Sleep Apnea; PSG = Polysomnography; PSS = Patient Satisfaction Survey; RCTs = Randomised Controlled Trails; UAS = Upper Airway Stimulation;*

[10] Stim = continued therapeutic stimulation, average amplitude 1.6 V ± 0.7; Sham = Stimulation voltage set at 0.1 V (as a subtherapeutic stimulation level and a deception for the patient)

Table A - 2: Study characteristics of non-randomized controlled trials (nRCTs) and observational studies

Study reference/ID (NCT) Author, year Funding	Sites or regions, countries, time of study	Study type	Intervention [number of patients enrolled] Name of device	Patient population Clinical stage	Endpoints Length of Follow-up
NCT01186926 NCT01211444 Kezirian et al., 2014 [27]	Australia 4 sites USA 4 sites 2010 - 2013	Multicentre prospective single-arm open-label study	UAS [31 patients] HGNS®; Apnex Medical, St Paul, MN, USA	Moderate-to-severe OSA Documented failure of PAP, Exclusion criteria: BMI >40 kg/m^2 and previous surgery	AHI and FOSQ, SAE mean change for and other PSG and symptom measures Usage: proportion of nights with use and h/night Follow-up: 6 months and 12 months
NCT01161420 Woodson et al., 2018 [28] Industry-supported multicentre academic and clinical setting: Inspire Medical Systems	Belgium 1 site France 2 sites Germany 3 sites The Netherlands 1 site USA 15 sites 2010 - 2017 *November 2010-February 2012 (recruitment)*	Multicentre prospective single-arm open-label study	UAS [126 patients] Inspire Medical Systems, Inc., Maple Grove, Minnesota	Moderate-to-severe OSA Intolerance or inadequate adherence to CPAP, Exclusion criteria: BMI >32 kg/m^2	ESS, FOSQ, Intrusive snoring, as reported by participant and bed partner Sleep-disordered breathing Follow-up: 12, 24, 36, 48 and 60 months
NCT03048604 Eastwood et al., 2020 [29]	Australia 4 sites France 3 sites UK 1 site (not enrolment) April 2017 - February 2018	Multicentre prospective single-arm open-label study	UAS [27 patients] Genio™ system (Nyxoah SA, Mont-Saint-Guibert, Belgium)	Moderate-to-severe OSA, Intolerance or inadequate adherence to CPAP Exclusion criteria: BMI >32 kg/m^2	Device-related SAE, AHI, ODI Follow-up: 6 months
NCT02293746 Steffen et al., 2019 [30]	Germany 3 sites July 2014– December 2016	Phase IV, follow up-post market study	UAS [60 patients] Inspire Medical Systems, Inc., Maple Grove, Minnesota	Moderate-to-severe OSA, Intolerance to PAP, Exclusion criteria: BMI >35 kg/m^2	ESS, BMI, UAS usage, AHI, ODI Follow-up: 24, 36 months
NCT02293746 Hofauer et al., 2019 [31]	Germany 2 sites July 2014 - December 2016	Phase IV, follow up-post market study	UAS [102 patients] Inspire Medical Systems, Inc., Maple Grove, Minnesota	Moderate-to-severe OSA, Intolerance to PAP, Exclusion criteria: BMI >35 kg/m^2	Objective and self-reported adherence to UAS Follow-up: average 10.1 months before the study of adherence
NCT01796925 Friedman et al., 2016 [33]	7 centres: USA, Germany, Belgium April – September 2013	Prospective, multicentre, single-arm feasibility study	THN [46 patients] ImThera aura6000™ system	Exclusion criteria: ≥10% central sleep Apnea, Clinical disease patterns[11], Evidence of positional OSA, Other active implanted medical devices	AHI, ODI, AE (short and long term), ArI, ESS, SAQLI Follow-up: 6 months
NCT02907398 Thaler et al., 2019 [32]	USA, Europe multicentre October 2016 - February 2019.	Multicentre, prospective, observational study	UAS [640, 6 months; 382, 12 months patients] Inspire Medical Systems, Inc., Maple Grove, Minnesota	Moderate-to-severe OSA (AHI 15 to 65 events/h), Intolerance or inadequate adherence to CPAP,	AHI, ESS, AE Follow-up: 6 months and 12 months

[11] clinically enlarged tonsils (3+ or 4+), Modified Mallampati IV, presence of nasal obstruction, syndromic craniofacial abnormalities, epiglottic obstruction

Study reference/ID (NCT) Author, year Funding	Sites or regions, countries, time of study	Study type	Intervention [number of patients enrolled] Name of device	Patient population Clinical stage	Endpoints Length of Follow-up
				Free of complete concentric collapse during DISE	
NCT02907398 Suurna et al., 2021 [18]	43 global centres October 2016 - March 2020	Multicentre, prospective, observational, registry study	UAS [1019, 1 year, 823 final follow-up completed] Inspire Medical Systems, Inc., Maple Grove, Minnesota	Moderate-to-severe OSA (AHI 15 to 65 events/h), Less than 25 % central/mixed apneas, Intolerance or failure of CPAP, Absence of complete concentric collapse during DISE Exclusion criteria: Life expectancy <1 year Clinical deems that patient is unfit for participation in the study	AHI, ESS, CGI, Therapy Usage (h/day), Therapy Response, PSS, AE Follow-up: at 3 – 6 months followed by annual visits
NCT02907398 Mehra et al., 2020 [17]	USA 6 sites Germany 3 sites October 2017 - January 2019	Multinational, prospective, experimental, parallel-arm study	UAS [250 patients] compared with no therapy [100 patients] Inspire Medical Systems, Dolden Valley, MN, USA	Patients with AHI 15 and 65 vents/h, Less than 25 % central and mixed apneas, PAP intolerance Absence of complete concentric collapse during DISE Exclusion criteria: Life expectancy <1 year Clinical deems that patient is unfit for participation in the study	AHI, ESS, FOSQ-10, ODI-4 %, Therapy Usage, CGI, Sa_{o2}, Percent recording time with Sa_{O2} < 90 % Follow-up: 6 months and 12 months

Abbreviations: *AHI = Apnea Hypopnea Index; approx. = approximately; Arl= Arousal Index; BMI = Body Mass Index; CGI-I = Clinical Global Impression of Improvement; CPAP = Continuous Positive Airway Pressure; DISE = Drug-Induced Sleep Endoscopy; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; HGNS = Hypoglossal Nerve Stimulation; h = hour; ODI = Oxygen Desaturation Index; OSA = Obstructive Sleep Apnea; PAP = Positive Airway Pressure; PSG = Polysomnography; PSS = Patient Satisfaction Survey; SAE = Serious Adverse Events; Sa_{o2} = Nadir arterial oxygen saturation; SQALI = Sleep Apnea Quality of Life Index; THN = Targeted hypoglossal neurostimulation; UAS = Upper Airway Stimulation*

Table A - 3: Patient characteristics and results on effectiveness and safety from RCTs and comparative nRCT[12]

Study reference/ID **Characteristics** **Category**	**NCT01161420;** **Woodson et al 2014 [26]** RCT (with only UAS responders) withdrawal study based on observational cohort study [126 patients] Strollo et al. 2014 [41]		**NCT03760328** **Heiser et al., 2021 [16]** RCT (with cross-over design)		**NCT02907398** **Mehra et al., 2020 [17]** nRCT (parallel-arm study)	
Patient characteristics						
Intervention vs. Comparator	N = 23 (OSA responders)	N = 23 (OSA responders)	N = 45 (Stim-Sham)	N = 44 (Sham – Stim)	N = 230	N = 100
Age [years], mean (SD)	57.1 ± 10.0	52.7 ± 10.4	58.3 ± 9.4	56.6 ± 10.4	57.5 ± 10.8	57.3 ± 8.4
Gender male %	95.6	82.6	82.2	79.5	84	70
BMI, kg/m2	28.4 ± 2.4	27.3 ± 2.4	28.6 ± 3.7	29.5 ± 3.9	29.8 ± 3.9	29.3 ± 3.9
Apnea hypopnea index (AHI) (SD)	31.3 ± 12.3	30.1 ± 11.4	32.1 ± 9.8	31.9 ± 11.4	33.7 ± 13.4	34.9 ± 16.4
Oxygen Desaturation index (ODI) (SD)	26.7 ± 13.0	26.8 ± 10.2	--	--	--	--
Percentage Sleep SaO2 <90 % (SD)	7.4 ± 8.3	5.6 ± 4.4	--	--	--	--
Functional Outcomes of Sleep Questionnaire (FOSQ) (SD)	15.1 ± 3.1	13.9 ± 2.6	--	--	--	--
Epworth Sleepiness Scale (ESS) (SD)	11.2 ± 5.3	11.3 ± 5.0	10.0 ± 4.7	10.0 ± 4.7	12.3 ± 5.5	10.9 ± 5.4
Neck size [cm] (SD)	41.6 ± 2.1	40.9 ± 3.6	--	--	--	--
Ethnicity (%)	--	--	Caucasian (100)	Caucasian (100)	White (99)	White (98)
Effectiveness Outcomes						
I vs. C (n pts)	OSA ON (23) vs. OSA OFF for 1 week (23)		Stim-Sham (45) vs. Sham (44) Crossover after 1 week		UAS (230) vs. no therapy (100)	
Apnea Hypopnea Index (AHI)						
After one week intervention	NR vs. NR		AHI-responders 1st week:		NR vs. NR	
Differences after 1 week (SD/95% CI)	1.7 ± 6.4 vs. 18.2 ± 15.6		33/45 (73%) vs. 13/44 (43.8%)		NR vs. NR	
Difference of change 1 week (SD/95% CI)	16.4 (9.2, 23.7, **p<0.001**		43.8% (25.1, 62.5), **p<0.001**		--	
12 months	7.2 ± 5.0 vs. 7.6 ±4.0, p = 0.74		--		14.7 ± 13.8 (228) vs. 26.8 ± 17.6 (100),	
Final visit I vs. C (n pts)	At 18 months: 9.6 ± 11.3 vs. 10.7 ± 7.3, p = 0.85		AHI after crossover 2nd week		**p<0.001**	
Difference of change final visit I vs. C (95% CI)	12 m-18 m: 0.2 (-5.1, 5.4), p = 0.69		(86 Stim pts. vs. 86 Sham pts.):		-19.1 ± 15.8 vs. -8.1 ± 20.9, **p<0.001**	
			0.5 (-1.2, 2.3) vs. 8.9 (7.2, 10.7), **p<0.001**			
Hypoxia Time (HAT) Percent Time SaO2 < 90 %						

[12]Extracted from the EUnetHTA report [1] and extended by the newly included studies

After one week intervention Differences after one week (SD/95 % CI) Difference of change 1 week (SD/95 % CI) 12 months Final visit I vs. C (n pts) Difference of change final visit I vs. C (95 % CI)	NR vs. NR -1.0 ± 6.4 vs. - 6.5 ± 10.8 5.4 (0.1, 10.7) p<0.04 3.2 ± 8.3 vs. 1.0 ± 2.0, p=0.23 At 18 months: 7.6 ± 17.8 vs. 1.7 ± 6.2, p=0.12 12 m-18 m: -4.6 ± 16.4 vs. -0.7 ± 2.0, p=0.26	NR vs. NR NR vs. NR NR vs. NR -- HAT after crossover 2nd week (86 Stim pts. vs. 86 Sham pts.) 2.4 (-1.7, 6.4) vs. 9.0 (4.9, 13.0) -6.6 (11.2, -2.0) p=0.005	NR vs. NR NR vs. NR -- 17.7 ± 25.7 (135) vs. 14.6 ± 22.9 (98), p=0.98 NR vs. NR
Oxygen Desaturation Index (ODI)			
After one week intervention Differences after one week (SD/95 % CI) Difference of change 1 week (SD/95 % CI) 12 months Final visit I vs. C (n pts) Difference of change final visit I vs. C (95 % CI)	NR vs. NR 1.6 ± 5.8 vs. 17.0 ±14.5 15.4 (8.7, 22.1), **p <0.001** 6.3 ±5.4 vs. 6.0± 3.7, p=0.81 At 18 months: 8.6±11.0 vs. 9.1 ±6.1, p=0.86 12 m-18 m: -1.9 ±19.0 vs. -3.1 ± 6.5, p=0.62	NR vs. NR NR vs. NR NR vs. NR -- ODI after crossover 2nd week (86 Stim pts. vs. 86 Sham pts.) 0.6 (-1.9, 3.0) vs. 12.7 (10.3, 15.2) -12.2 (-14.8, -9.6) **p <0.001**	NR vs. NR NR vs. NR -- 14.1 ± 14.1 (219) vs. 25.5 ± 17.9 (96) **p<0.001** NR vs. NR
Functional Outcomes of Sleep Questionnaire (FOSQ)			
After one week intervention Differences after one week (SD/95 % CI) Difference of change 1 week (SD/95 % CI) 12 months Final visit I vs. C (n pts) Difference of change final visit I vs. C (95 % CI)	NR vs. NR 0.0 ± 1.0 vs. 2.3 ± 3.0 -2.3 (-3.8, -0.9), **p=0.001** 17.9 ±2.9 vs. 17.0 ± 3.5, p=0.36 At 18 months: 18.0 ± 2.9, p=0.29 12 m-18 m: -0.1 ± 1.6 vs. 0.0 ± 2.3, p=0.91	NR vs. NR NR vs. NR NR vs. NR -- FOSQ after crossover 2nd week (86 Stim pts. vs. 86 Sham pts.) 17.0 ± 3.2 vs. 14.9 ± 4.6 2.1 (1.4, 2.8), **p<0.001**	NR vs. NR NR vs. NR -- 17.1 ± 3.2 (221) vs. 12.4 ± 3.7 (75), **p<0.001** NR vs. NR
Epworth Sleepiness Scale (ESS)			
After one week intervention Differences after one week (SD/95 % CI) Difference of change 1 week (SD/95 % CI) 12 months Final visit I vs. C (n pts) Difference of change final visit I vs. C (95 % CI)	NR vs. NR 0.3 ± 1.8 vs. -3.8 ± 4.6 4.2 (2.0, 6.4), **p<0.001** 5.9 ± 3.4 vs. 6.9 ±4.6, p=0.43 At 18 months: 6.0 ±3.7 vs. 8.0 ± 4.4, p=0.09 12 m-18 m: -0.1 ± 2.4 vs. -1.3 ± 4.6, p=0.26	NR vs. NR NR vs. NR NR vs. NR -- ESS after crossover 2nd week (86 Stim pts. vs. 86 Sham pts.) 7.5 ± 4.9 vs. 12.0 ± 4.3 -3.3 (-4.4, -2.2), **p<0.001**	NR vs. NR NR vs. NR -- 7.2 ± 4.8 (226) vs. 12.8 ± 5.2 (90), **p<0.001** -5.1 ± 5.5 vs. 1.8 ± 3.7, **p<0.001**
Clinical Global Impression (CGI) scale and treatment effect			

Improvement in intervention-group (%) Patient Satisfaction (%)	NR	76.7 NR	93 95
Adherence to treatment			
UAS adherence (months)	NR	33.9 ± 22.6 vs. 26.4 ± 15.4, p=0.07	5.6 ± 2.0 h/night
Safety Outcomes			
Cardiovascular Events	NR	One stroke suffered by one participant during the time period of stimulation ON, was deemed unrelated to UAS	NR
Serious adverse event			
Device-related Procedure-related (n events in n patients)	NR	NR	Device revision to reposition due to an uncomfortable stimulation lead position (2 in 1 patient)
Adverse events*			
Device-related Procedure-related (n events)	NR	NR	Swallowing or speech effects (1) Incision/Scar discomfort (3) Discomfort (device) (1) Other (snoring, bloody sputum) (2) Stimulation related (4) Tongue abrasions (6) Other discomfort (2) Residual OSA symptoms (4) Forgets to use device (1) Stimulation programming issue (1) Insomnia (1) Dry mouth (1) Unrelated dysapnea (1)
*One patient can have multiple events, at different points during follow-up			
Abbreviations: *AHI = Apnea Hypopnea Index; BMI = Body Mass Index; C = Comparator; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; HGNS = Hypoglossal Nerve Stimulation; I = Intervention, n = Number; N = Number of patients; NR = Not Reported; nRCT = non Randomised Controlled Trail; ODI = Oxygen Desaturation index; UAS = Upper Airway Stimulation; RCT = Randomised Controlled Trail; SD = Standard Deviation;*			

Table A - 4: Patient characteristics and results on safety from observational studies [13]

Study reference/ ID **Characteristics** **Category**	**NCT01186926; NCT01211444;** Kezirian et al. 2014 [27]	**NCT01161420; Woodson et al 2018 [28]** based on observational cohort study [126 patients] Strollo et al. 2014 [41]		**NCT03048604;** Eastwood et al 2020 [29]	**NCT02293746;** Steffen et al. 2019 [30]
Patient characteristics					
Intervention	N=31	N=12614	N=12615	N=27	N=60
Age [years], mean (SD)	52.4 ± 9.4	54.5 ± 10.2		55.9 ± 12.0	56.8 ± 9.1
Gender male %	65	83		63	97
BMI, kg/m2	32.4 ± 3.6	28.4 ± 28.5		27.4 ± 3.0	28.8 ± 3.6
Apnea hypopnea index (AHI) (SD)	45.4 ± 17.5	32.0 ± 11.8		23.7 ± 12.2	31.2 ± 13.2
Oxygen Desaturation index (ODI) (SD)	20.9 ± 17.3	28.9 ± 9.6		19.1 ± 11.2	28.5 ± 16.6
Percentage Sleep SaO2 <90 % (SD)	--	--		5.0 ± 6.0	--
Functional Outcomes of Sleep Questionnaire (FOSQ) (SD)	14.2 ± 2.0	14.3 ± 3.2		15.3 ± 3.3	--
Epworth Sleepiness Scale (ESS) (SD)	12.1 ± 4.6	11.6 ± 5.0		11.0 ± 5.3	12.4 ± 5.7
Neck size [cm] (SD)	--	--		39.0 ± 4.2 (n=24)	--
Ethnicity (%)	Non-Hispanic Caucasian (90)	--		Caucasian (88.9) Hispanic (11.1)	--
Safety Outcomes					
Cardiovascular Events	NR	NR	NR	NR	NR
Serious adverse event					
Device-related Procedure-related (n events in n patients)	Device explantation due to lack of sufficient effectiveness (2 in 2 patients) Device replacement due to dislodgement of stimulation lead cuff (2 in 2 patients) Device explantation due to infection (1 in 1 patient)	NR	Device replacement/re-position due to failures (9 in 8 patients)	Device explantation due to infection (3 in 2 patients) Impaired swallowing that led to a 1 day prolongation of hospitalization (1 in 1 patient)	Sensing lead replacement due to insulation damage at the movable anchor (1 in 1 patient) Sensing lead replacement (1 in 1 patient)
Adverse events*					
Device-related Procedure-related (n events)	Tongue abrasion (17)[ab] Numbness/pain at incision site (11)[ab]	Discomfort due to electrical stimulation (81) Tongue abrasion (28)	Discomfort due to electrical stimulation (61) Tongue abrasion (21)	Local skin irritation due to the disposable patch (9) Tongue abrasion (4)	

[13] extracted from the EUnetHTA report [1] and extended by the newly included studies
[14] 12 month follow-up
[15] 5 year follow-up

		Dry mouth (10) Mechanical pain associated with presence of the device (7) Temporary internal device usability or functionality complaint (12) Temporary external device usability or functionality complaint (11) Mild infection device related (1) Other acute symptoms (21)[e] Postoperative discomfort related to incisions (47) Postoperative discomfort independent of incisions (41) Temporary tongue weakness (34) Intubation effects (18) Headache (8) Other postoperative symptoms (22)[e] Mild infection (1)	Dry mouth (10) Mechanical pain associated with presence of the device (7) Temporary internal device usability or functionality complaint (13) Temporary external device usability or functionality complaint (34) Other acute Symptoms (18)[e] Postoperative discomfort related to incisions (5) Postoperative discomfort independent of incisions (1)	Tongue fasciculation (4) Discomfort due to electrical stimulation (3) Impairment or painful swallowing (8) Dysarthria (7) Haematoma (5) Swelling or bruising around the incision site (5) Abnormal scarring (5)	
*One patient can have multiple events, at different points during follow-up, [a] Patients, not events, [b] Only the most frequent non-serious adverse event is reported in the article, [c] Information on non-serious adverse events was not found in the study, [d] Postoperative other includes shortness of breath, seroma, numbness of the throat, hoarseness during the day, and a mild tongue-base and epiglotic obstruction, e It was not possible to classify or specified the adverse events					
Abbreviations: *AHI = Apnea Hypopnea Index; BMI = Body Mass Index; C = Comparator; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; I = Intervention, n = Number; N = Number of patients; nRCT = non Randomised Controlled Trail; NR = Not Reported; ODI = Oxygen Desaturation Index; UAS = Upper Airway Stimulation;SD = Standard Deviation;*					

Table A - 5: Patient characteristics and results on safety from observational studies[16]

Study reference/ ID Characteristics Category	NCT02293746; Hofauer et al. 2019 [31]	NCT01796925; Friedman et al. 2016 [33]	NCT02907398 Thaler et al. 2019 [32]	NCT02907398 Suurna et al. 2021 [18]
Patient characteristics				
Intervention	N=102	N=46	N=1017	N=1849
Age [years], mean (SD)	56.7 ± 11.3	54.9 ± 11.1 (35.3- 73.4)	60 ± 11	60.1 ± 10.9
Gender male %	--	94 (43/46)	74	73
BMI, kg/m2	29.4 ± 4.3	30.8 ± 3.7 (20.2 – 36.9)	29.3 ± 3.9	29.3 ± 3.9
Apnea hypopnea index (AHI) (SD)	32.8 ± 13.9	--	32.8 (23.6-45.0)17	36.0 ± 15.7
Oxygen Desaturation index (ODI) (SD)	27.6 ± 17.6	--	--	--
Percentage Sleep SaO2 <90 % (SD)	--	--	--	--
Functional Outcomes of Sleep Questionnaire (FOSQ) (SD)	--	--	--	--
Epworth Sleepiness Scale (ESS) (SD)	12.9 ± 4.6	--	11.4 ± 5.7	11.2 ± 5.6
Neck size [cm] (SD)	--	--	--	--
Ethnicity (%)	--	--	Caucasian (96)	Caucasian (95)
Safety Outcomes				
Cardiovascular Events	NR	NR	NR	Anaesthesia-related intraoperative arrest (1 in 1 patient)
Serious adverse event (SAE)				
Device-related Procedure-related (n events in n patients)	NR	Surgical intervention with replacement of lead due to lack of sufficient effectiveness (1 in 1 patient) Device migration (1 in 1 patient) Hematoma (1 in 1 patient) Pain (3 in 3 patients). In 2 patients required replacement of the pulse generator Bleeding (1 in 1 patient) Other (5 in 4 patients)e	Surgical intervention for device revision due to stimulation electrode dislodgement (1 in 1 patient) Surgical intervention for stimulation electrode repositioning (2 in 2 patients) Infection without device explantation (2)	Hematoma (2) Infection (1) Implant could not be placed on the right side (1) Intraoperative arrest (1) Obstructive event (1) Pneumothorax (1) Other – unrelated (1) System explant (2 or more components) (1)

[16] extracted from the EUnetHTA report [1] and extended by the newly included studies

[17] Interquartile range

				System revision (2 or more components) (3) Sensor lead revision (13) Stimulation lead revision (12) IPG pocket revision (2) Other (4)
Adverse events (AE)*				
Device-related Procedure-related (n events)	NR	Paresis (5) Paresthesia (6) Anesthesia complication (1) Hematoma (3) Infection (4) Pain (19) Other (17)[e]	Discomfort, device (15) Stimulation-related discomfort (69) Insomnia/arousal (27) Tongue abrasion (26) Device usability complaint related with activation (60) Infection without device explantation (2) Tongue weakness (3) Swallowing or speech related (5) Discomfort, incision/scar (22) Other discomfort (20) Postoperative, other (20)[d]	349 patients reported non-serious AE: Most common events: stimulation-related discomfort (8.2 %), insomnia/arousals (3.6%), and tongue abrasion/irritation (3.4%)
*One patient can have multiple events, at different points during follow-up, ** Only stated significant change from baseline, a Patients, not events, b Only the most frequent non-serious adverse event is reported in the article, c Information on non-serious adverse events was not found in the study, d Postoperative other includes shortness of breath, seroma, numbness of the throat, hoarseness during the day, and a mild tongue-base and epiglotic obstruction				
***Abbreviations**: AE = Adverse Events, AHI = Apnea Hypopnea Index; BMI = Body Mass Index; C = Comparator; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; I = Intervention, nRCT = non Randomised Controlled Trail; n = Number; N = Number of patients; NR = Not Reported; ODI = Oxygen Desaturation Index; SAE = Serious Adverse Events; UAS = Upper Airway Stimulation; SD = Standard Deviation;*				

Risk of bias tables

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [42] and in the Guidelines of EUnetHTA [43].

Table A - 6: Risk of bias – study level (randomised controlled crossover trail), see [2, 42]

Trial	Bias arising from the randomization process	Risk of Bias arising from period and carry over effects	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Heiser et al., 2021 [16]	Low[18]	Low[19]	Low[20]	High[21]	Some concern[22]	High[23]	High Risk

Table A - 7: Risk of Bias– study level of nRCT comparing UAS versus no therapy, see [3, 43]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in classification of intervention	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias
Mehra et al., 2020 [17]	Moderate[24]	Moderate[25]	Low[26]	Low[27]	Serious[28]	Serious[29]	Serious[30]	Serious

[18] "Each participant was randomised 1:1 to one oft two groups…using a centralised, computer-generated, password-protected system"
[19] "… no statistical evidence of a carryover effect…"
[20] No deviations that arose from the trail context – intention to treat analysis
[21] Outcomes are reported across groups and not after 1st week, 2nd week. No outcome data on SAE/ AE reported at all
[22] Participants and assessors were aware of the study arm allocation – critical for some subjective outcomes (ex. FOSQ)?
[23] For some results, only the difference from the baseline is published but not the baseline itself. Some results are only mentioned in the Abstract.
[24] Larger differences between the German and US locations in some variables – adjustment of the model for…did not appreciably influence – Differences in follow-up time UAS – no therapy
[25] If the insurer approved the request, the participant was assigned to the therapy arm – if insurer denied the patient was assigned to the comparator, start of intervention and follow up was different
[26] Intervention groups were clearly defined
[27] Any deviations from intended intervention reflected usual practice
[28] Missing data on outcomes at final visit
[29] Different measurement methods across the countries and before and after intervention, Assessors and Patients were aware of the intervention, lack of consistency of PSG versus HSAT
[30] The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results

Table A - 8: Risk of Bias– study level of case series, see [4]

Study reference/ID	Suurna, 2021 [18]
Study objective	
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes[31]
Study design	
2. Was the study conducted prospectively?	Yes[32]
3. Were the cases collected in more than one centre?	Yes[33]
4. Were patients recruited consecutively?	Yes[34]
Study population	
5. Were the characteristics of the patients included in the study described?	Yes[35]
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes[36]
7. Did patients enter the study at a similar point in the disease?	Unclear[37]
Intervention and co-intervention	
8. Was the intervention of interest clearly described?	Yes[38]
9. Were additional interventions (co-interventions) clearly described?	Yes[39]
Outcome measures	
10. Were relevant outcome measures established a priori?	Yes[40]
11. Were outcome assessors blinded to the intervention that patients received?	Unclear[41]
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes[42]

[31] The hypothesis/aim/objective of the study was clearly stated
[32] It is clearly stated that the study is prospective
[33] International, multicentre, observational registry
[34] "All patients who undergo implant of the UAS system are eligible to participate in the registry if they are willing to provide consent and have a life expectancy of at least one year"
[35] The characteristics of the patients are described
[36] Inclusion and exclusion criteria are stated
[37] No clear information about the time point of entry
[38] The interest of the intervention is clearly described
[39] Co-interventions are listed
[40] Relevant outcome measures were established a priori
[41] No information about the blinding of the assessors
[42] The methods for the outcome measurement was appropriate

Study reference/ID	Suurna, 2021 [18]
13. Were the relevant outcome measures made before and after the intervention?	Yes[43]
Statistical Analysis	
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes[44]
Results and Conclusions	
15. Was the follow-up lentght reported?	Yes[45]
16. Were losses to follow-up reported?	No[46]
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	No[47]
18. Were the adverse events reported?	Yes[48]
19. Were the conclusions of the study supported by results?	Yes[49]
Competing interests and sources of support	
20. Were both competing interests and sources of support for the study reported?	Yes[50]
Overall Risk of bias	17/20 Moderate Risk

[43] Relevant outcome measures were made before and after the intervention
[44] Appropriate statistical tests were used
[45] Follow-up length was reported (annual visits)
[46] No data for low of follow up patients (no information why loss of follow up)
[47] Only mean and median are given
[48] Adverse events were reported
[49] The conclusion is supported by the results
[50] Both are reported

List of ongoing randomised controlled trials

Table A - 9: List of ongoing RCTs of HGNS

Identifier/ Trial name	Studydesign	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor	Status
NCT04950894 Treating Obstructive Sleep Apnea Using Targeted Hypoglossal Neurostimulation (OSPERY)	Multi-center, open-label, prospective, randomized clinical trial	150 participants	HGN therapy activation at Month 1 - compared at Month 7 to Control group aura6000(R) System	HGN therapy NOT activated at Month 1 - compared at Month 7 to Active group	Rate of response to therapy Rate of all serious adverse device/procedure related events	January 2023	LivaNova	recruiting
NCT02263859 Targeted Hypoglossal Neurostimulation Study #3 (THN3)	Randomised, parallel-arm study	138 participants	aura6000 System implanted and therapy turned ON at the Month 1 follow-up visit	aura6000 System and receive treatment as-usual	Improvement in Apnea Hypopnea Index (AHI) Improvement in Oxygen Desaturation Index (ODI) Safety Analysis	December 2022	LivaNova	Active, not recruiting
NCT03359096 HGNS on Cardiovascular Outcomes (CARDIOSA-12)	Randomised controlled, crossover trail	63 participants	Therapeutic Hypoglossal Nerve Stimulation (HGNS)	Sham Comparator: Subtherapeutic 'Sham' HGNS	Change in mean 24-HOUR systolic ambulatory blood pressure values	Completed January 28, 2022	University of Pennsylvania American Heart Association American Academy of Sleep Medicine	Completed no results available yet

Abbreviations: *AHI = Apnea Hypopnea Index; HGN = Hypoglossal Nerve; HGNS = Hypoglossal Nerve Stimulation, ODI = Oxygen Desatu-ration index; RCT = Randomised Controlled Trail, THN = Targeted Hypoglossal Neurostimulation*

Literature search strategies

Search strategy for Cochrane

Search Name:	Upper airway stimulation for moderate-to-severe sleep apnea
Search date:	28.12.2021
ID	Search
#1	MeSH descriptor: [Sleep Apnea Syndromes] explode all trees
#2	MeSH descriptor: [Snoring] explode all trees
#3	"sleep apnea*" (Word variations have been searched)
#4	"sleep apnoea*" (Word variations have been searched)
#5	(OSA):ti,ab,kw
#6	snore* (Word variations have been searched)
#7	snoring (Word variations have been searched)
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	MeSH descriptor: [Cranial Nerves] explode all trees
#10	MeSH descriptor: [Electric Stimulation] explode all trees
#11	MeSH descriptor: [Electric Stimulation] explode all trees
#12	#10 OR #11
#13	#9 AND #12
#14	((crani* OR hypogloss*) NEAR stimulat*) (Word variations have been searched)
#15	(nerve* NEAR stimulat*) (Word variations have been searched)
#16	(hypogloss* crani* nerve stimulat*) (Word variations have been searched)
#17	(hypo-gloss* crani* nerve stimulat*) (Word variations have been searched)
#18	HNS:ti,ab,kw (Word variations have been searched)
#19	#13 OR #14 OR #15 OR #16 OR #17 OR #18 (Word variations have been searched)
#20	#8 AND #19
#21	#8 AND #19 with Cochrane Library publication date Between Nov 2018 and Dec 2021
#22	#8 AND #19 with Publication Year from 2018 to 2021, in Trials
#23	#21 OR #22
#24	(conference abstract):pt (Word variations have been searched)
#25	(abstract):so (Word variations have been searched)
#26	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR regis-troclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so (Word variations have been searched)
#27	#24 OR #25 OR #26
#28	#23 NOT #27
Total hits:	19

Search strategy for INAHTA

Search Name:	Upper airway stimulation for moderate-to-severe sleep apnea
Search date:	28.12.2021
#1	"Sleep Apnea Syndromes"[mhe],"91","2021-12-28T16:36:47.000000Z"
#2	"sleep apnea*","76","2021-12-28T16:37:27.000000Z"
#3	"sleep apnoea*","23","2021-12-28T16:37:35.000000Z"
#4	snore,"1","2021-12-28T16:38:07.000000Z"
#5	snoring,"8","2021-12-28T16:38:14.000000Z"
#6	(OSA)[Title] OR (OSA)[abs],"32","2021-12-28T16:38:46.000000Z"
#7	((OSA)[Title] OR (OSA)[abs]) OR (snoring) OR (snore) OR ("sleep apnoea*") OR ("sleep apnea*") OR ("Sleep Apnea Syndromes"[mhe]),"109","2021-12-28T16:38:55.000000Z"
#8	"Cranial Nerves"[mhe],"31","2021-12-28T16:39:29.000000Z"
#9	"Electric Stimulation"[mhe],"277","2021-12-28T16:40:01.000000Z"
#10	"Electric Stimulation Therapy"[mhe],"248","2021-12-28T16:40:16.000000Z"
#11	("Electric Stimulation Therapy"[mhe]) OR ("Electric Stimulation"[mhe]),"277","2021-12-28T16:40:26.000000Z"
#12	(("Electric Stimulation Therapy"[mhe]) OR ("Electric Stimulation"[mhe])) AND ("Cranial Nerves"[mhe]),"21","2021-12-28T16:40:39.000000Z"
#13	(crani* OR hypogloss*) AND (stimulat*),"8","2021-12-28T16:41:26.000000Z"
#14	(nerve*) AND (stimulat*),"116","2021-12-28T16:42:11.000000Z"
#15	(HNS)[Title] OR (HNS)[abs],"2","2021-12-28T16:42:54.000000Z"
#16	((HNS)[Title] OR (HNS)[abs]) OR ((nerve*) AND (stimulat*)) OR ((crani* OR hypogloss*) AND (stimu-lat*)) OR ((("Electric Stimulation Therapy"[mhe]) OR ("Electric Stimulation"[mhe])) AND ("Cranial Nerves"[mhe])),"118","2021-12-28T16:43:24.000000Z"
#17	(((HNS)[Title] OR (HNS)[abs]) OR ((nerve*) AND (stimulat*)) OR ((crani* OR hypogloss*) AND (stimulat*)) OR ((("Electric Stimulation Therapy"[mhe]) OR ("Electric Stimulation"[mhe])) AND ("Cranial Nerves"[mhe]))) AND (((OSA)[Title] OR (OSA)[abs]) OR (snoring) OR (snore) OR ("sleep apnoea*") OR ("sleep apnea*") OR ("Sleep Apnea Syndromes"[mhe])),"6","2021-12-28T16:43:54.000000Z"
#18	((((HNS)[Title] OR (HNS)[abs]) OR ((nerve*) AND (stimulat*)) OR ((crani* OR hypogloss*) AND (stim-ulat*)) OR ((("Electric Stimulation Therapy"[mhe]) OR ("Electric Stimulation"[mhe])) AND ("Cranial Nerves"[mhe]))) AND (((OSA)[Title] OR (OSA)[abs]) OR (snoring) OR (snore) OR ("sleep apnoea*") OR ("sleep apnea*") OR ("Sleep Apnea Syndromes"[mhe]))) FROM 2018 TO 2021,"3","2021-12-28T16:47:53.000000Z"
#19	(((((HNS)[Title] OR (HNS)[abs]) OR ((nerve*) AND (stimulat*)) OR ((crani* OR hypogloss*) AND (stimulat*)) OR ((("Electric Stimulation Therapy"[mhe]) OR ("Electric Stimulation"[mhe])) AND ("Cra-nial Nerves"[mhe]))) AND (((OSA)[Title] OR (OSA)[abs]) OR (snoring) OR (snore) OR ("sleep apnoea*") OR ("sleep apnea*") OR ("Sleep Apnea Syndromes"[mhe]))) FROM 2018 TO 2021) AND (English OR German)[Language],"2","2021-12-28T16:48:14.000000Z"
Total hits:	2

Search strategy for EMBASE

Search Name:	Upper airway stimulation for moderate-to-severe sleep apnea
Search date	28.12.21
#1.	'sleep disordered breathing'/exp
#2.	'sleep apnea*'
#3.	'sleep apnoea*'
#4.	osa:ti,ab
#5.	'snoring'/exp

#6.	snore*
#7.	snoring
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9.	'cranial nerve'/exp
#10.	'electrostimulation'/exp
#11.	'electrostimulation therapy'/exp
#12.	#10 OR #11
#13.	#9 AND #12
#14.	(crani* OR hypogloss* OR 'hypo-gloss*') NEAR/5
	stimulat*
#15.	nerve* NEAR/5 stimulat*
#16.	hns:ab,ti
#17.	#13 OR #14 OR #15 OR #16
#18.	#8 AND #17
#19.	#18 AND ([controlled clinical trial]/lim OR
	[randomized controlled trial]/lim)
#20.	'randomized controlled trial'/de
#21.	'controlled clinical trial'/de
#22.	random*:ti,ab,tt
#23.	'randomization'/de
#24.	'intermethod comparison'/de
#25.	placebo:ti,ab,tt
#26.	compare:ti,tt OR compared:ti,tt OR
	comparison:ti,tt
#27.	(evaluated:ab OR evaluate:ab OR evaluating:ab OR
	assessed:ab OR assess:ab) AND (compare:ab OR
	compared:ab OR comparing:ab OR comparison:ab)
#28.	(open NEXT/1 label):ti,ab,tt
#29.	((double OR single OR doubly OR singly) NEXT/1
	(blind OR blinded OR blindly)):ti,ab,tt
#30.	'double blind procedure'/de
#31.	(parallel NEXT/1 group*):ti,ab,tt
#32.	crossover:ti,ab,tt OR 'cross over':ti,ab,tt
#33.	((assign* OR match OR matched OR allocation)
	NEAR/6 (alternate OR group OR groups OR
	intervention OR interventions OR patient OR
	patients OR subject OR subjects OR participant OR
	participants)):ti,ab,tt
#34.	assigned:ti,ab,tt OR allocated:ti,ab,tt
#35.	(controlled NEAR/8 (study OR design OR
	trial)):ti,ab,tt

#36.	volunteer:ti,ab,tt OR volunteers:ti,ab,tt
#37.	'human experiment'/de
#38.	trial:ti,tt
#39.	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR
	#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR
	#34 OR #35 OR #36 OR #37 OR #38
#40.	((random* NEXT/1 sampl* NEAR/8 ('cross section*'
	OR questionnaire* OR survey OR surveys OR
	database OR databases)):ti,ab,tt) NOT
	OR 'randomised controlled':ti,ab,tt OR
	'randomized controlled':ti,ab,tt OR 'randomly
	assigned':ti,ab,tt)
#41.	'cross-sectional study' NOT ('randomized
	controlled trial'/de OR 'controlled clinical
	study'/de OR 'controlled study'/de OR 'randomised
	controlled':ti,ab,tt OR 'randomized
	controlled':ti,ab,tt OR 'control group':ti,ab,tt
	OR 'control groups':ti,ab,tt)
#42.	'case control*':ti,ab,tt AND random*:ti,ab,tt NOT
	('randomised controlled':ti,ab,tt OR 'randomized
	controlled':ti,ab,tt)
#43.	'systematic review':ti,tt NOT (trial:ti,tt OR
	study:ti,tt)
#44.	nonrandom*:ti,ab,tt NOT random*:ti,ab,tt
#45.	'random field*':ti,ab,tt
#46.	('random cluster' NEAR/4 sampl*):ti,ab,tt
#47.	review:ab AND review:it NOT trial:ti,tt
#48.	'we searched':ab AND (review:ti,tt OR review:it)
#49.	'update review':ab
#50.	(databases NEAR/5 searched):ab
#51.	(rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR
	mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR
	murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR
	pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR
	rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR
	dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR
	bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR
	trout:ti,tt OR marmoset*:ti,tt) AND 'animal
	experiment'/de
#52.	'animal experiment'/de NOT ('human experiment'/de
	OR 'human'/de)

#53.	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR
	#47 OR #48 OR #49 OR #50 OR #51 OR #52
#54.	#39 NOT #53
#55.	#18 AND #54
#56.	#18 AND ([cochrane review]/lim OR [systematic
	review]/lim OR [meta analysis]/lim)
#57.	('meta analysis'/exp OR 'systematic review'/exp
	OR ((meta NEAR/3 analy*):ab,ti) OR
	metaanaly*:ab,ti OR review*:ti OR overview*:ti OR
	((synthes* NEAR/3 (literature* OR research* OR
	studies OR data)):ab,ti) OR (pooled AND
	((synthes* NEAR/3 (literature* OR research* OR
	analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti)
	AND studies:ab,ti) OR medline:ab,ti OR
	medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR
	scisearch:ab,ti OR psychinfo:ab,ti OR
	psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti
	OR cinhal:ab,ti OR cancerlit:ab,ti OR
	cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR
	ovid:ab,ti OR (((hand OR manual OR database* OR
	computer*) NEAR/2 search*):ab,ti) OR ((electronic
	NEAR/2 (database* OR 'data base' OR 'data
	bases')):ab,ti) OR bibliograph*:ab OR 'relevant
	journals':ab OR (((review* OR overview*) NEAR/10
	(systematic* OR methodologic* OR quantitativ* OR
	research* OR literature* OR studies OR trial* OR
	record* OR case* OR patient*) NEAR/2
	review*):ab,ti) OR (((patient* OR review*) NEAR/2
	chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR
	mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR
	hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti
	OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR
	cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT
	('editorial'/exp OR 'erratum'/de OR 'letter'/exp)
	NOT (('animal'/exp OR 'nonhuman'/exp) NOT
	(('animal'/exp OR 'nonhuman'/exp) AND
	'human'/exp))
#58.	#18 AND #57
#59.	#19 OR #55 OR #56 OR #58
#60.	#59 AND [1-11-2018]/sd NOT [29-12-2021]/sd
#61.	#59 AND [1-11-2018]/sd NOT [29-12-2021]/sd AND

	([english]/lim OR [german]/lim)
#62.	#61 AND 'Conference Abstract'/it
#63.	#61 NOT #62
Total hits:	106

Search strategy for Medline

Search Name:	Upper airway stimulation for moderate-to-severe sleep apnea
Search date:	28.12.21
#1	exp Sleep Apnea Syndromes/ (49563)
#2	sleep apn?ea*.mp. (67252)
#3	snore*.mp. (2178)
#4	snoring.mp. (10070)
#5	OSA.ti,ab. (24035)
#6	1 or 2 or 3 or 4 or 5 (73047)
#7	exp Cranial Nerves/ (124839)
#8	exp Electric Stimulation/ (134291)
#9	exp Electric Stimulation Therapy/ (105342)
#10	8 or 9 (236700)
#11	7 and 10 (12522)
#12	((crani* or hypogloss*) adj5 stimulat*).mp. (1743)
#13	(nerve* adj5 stimulat*).mp. (55459)
#14	HNS.ti,ab. (2021)
#15	11 or 12 or 13 or 14 (65380)
#16	6 and 15 (892)
#17	16 (892)
#18	limit 16 to clinical trial, all (57)
#19	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug thera-py.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (5828837)
#20	16 and 19 (208)
#21	limit 16 to (meta analysis or "systematic review") (32)
#22	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 ex-tract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (863704)
#23	16 and 22 (63)
#24	18 or 20 or 21 or 23 (273)
#25	limit 24 to dt=20181101-20211228 (135)
#26	limit 25 to (english or german) (133)
#27	remove duplicates from 26 (70)
Total hits:	70

HTA Austria
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