Upper Airway Stimulation for Moderate-to-Severe Sleep Apnea

Systematic Review
Final

Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document No. 100
ISSN online: 1998-0469

Upper Airway Stimulation for Moderate-to-Severe Sleep Apnea

Systematic Review
Final

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, March 2016

Project Team

Project leader: Dr. Agnes Kisser

Authors: 1. DDr. Irmgard Schiller-Frühwirth MPH
2. Dr. Agnes Kisser

Project Support

Systematic literature search: Tarquin Mittermayr, BA

External Review: OA Dr. Thomas J. Schmal; Barmherzige Brüder Wien

Internal Review: PD. Dr. Claudia Wild

Correspondence

Agnes Kisser, agnes.kisser@hta.lbg.ac.at

This report should be referenced as follows:

Schiller-Frühwirth I, Kisser A. Upper Airway Stimulation for Moderate-to-Severe Sleep Apnea. Decision Support Document No. 100; 2016. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.imce.org).

Disclaimer

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

The HTA Core Model®, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: HTA Core Model 3.0. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

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.

Content Information

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Wien
http://hta.lbg.ac.at/page/imprint

Responsible for content:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at

Decision Support Document No.: 100

ISSN-online: 1998-0469

Content

List of Figures

List of tables

List of abbreviations

AE ..... Adverse event
AHI ..... Apnea-hypopnea index
BMI ..... Body mass index
CI ..... Confidence interval
CPAP ..... Continuous positive airway pressure
DIESE ..... Drug-induced sleep endoscopy
ESS ..... Epworth Sleepiness Scale
FDA ..... Food and Drug Administration
FOSQ ..... Functional Outcomes of Sleep Questionnaire
H(G)NS ..... Hypoglossal nerve stimulation
IPG ..... Implanted pulse generator
LBI-HTA ..... Ludwig Boltzmann Institute
NREM ..... Non-rapid eye movement sleep
ODI ..... Oxygen desaturation index
OSA(S) ..... Obstructive sleep apnea (syndrome)
RCT ..... Randomised controlled trial
SADE ..... Serious device related adverse effect
SAE ..... Serious adverse event
SD ..... Standard deviation
AUS ..... Upper airway stimulation

Summary

Introduction

Health Problem

Obstructive sleep apnea (OSA) is a potentially serious sleep disorder in which breathing repeatedly stops and starts during sleep. It results from an upper airway collapse during sleep that occurs because of an inadequate motor tone of the tongue and/or airway dilator muscles and is associated with intermittent hypoxia and transient arousals. Collapsibility can also be increased by underlying anatomic alterations. Obesity and particularly central adiposity, both potent risk factors for sleep apnea, can increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues [1].

obstruktive Schlafapnoe (OSA): schlafbezogene Atmungsstörung durch Kollaps der Rachenmuskulatur

Symptoms include snoring, witnessed apneas and daytime sleepiness. OSA has well-established neurocognitive and cardiovascular sequelae [2]. If left untreated, it leads to excessive daytime sleepiness, cognitive dysfunction, impaired work performance and decrements in health-related quality of life [3]. The condition is associated with increased risk of traffic accidents, diabetes, hypertension, coronary artery disease and stroke.

Symptome: Tagesmüdigkeit, Atemaussetzer, Leistungsabfall, depressive Symptome

The apnea-hypopnea index (AHI) is commonly used to categorize the severity of OSA and it represents the average number of apneas and/or hypopneas per hour of recorded sleep.

Apnoe-Hypopnoe-Index: Hinweis auf Schwere der OSA

The standard first-line OSA treatment involves continuous positive air-way pressure (CPAP) devices, which deliver compressed air into the air-way to keep it open. [4]. Treatment effectiveness is limited by variable adherence to prescribed therapy. When only CPAP therapy is considered, a certain portion of the sleep apnea population remains inadequately treated.

Standardtherapie: CPAP

Description of Technology

A number of factors contribute to OSA pathogenesis, including decreased tone during sleep in the upper airway dilator muscles, especially the genioglossus [5]. This notion has led to investigations of direct electrical stimulation of the motor nerve innervating the genioglossus muscle, the hypoglossal nerve (HGN) [6-8]. The technology utilises an implantable device that electrically stimulates the hypoglossal nerve, leading to the contraction of the genioglossus muscle, the major muscle responsible for tongue protrusion. Theoretically, increasing the activity in the pharyngeal dilator muscles could be effective for patients who have a dysfunction in these muscles.

elektrische Stimulation des Nervus hypoglossus – Tonisierung des Atemwegsöffners M.genioglossus

Methods

Answering the research questions regarding efficacy and safety-related outcomes was based on a systematic literature search from different databases. The study selection, data extraction and assessing the methodological quality of the studies was performed by two review authors (ISF, AK) independently from each other.

systematischer Literaturreview

Domain effectiveness

Wirksamkeit: Schweregrad der OSA Tagesschläfrigkeit und Lebensqualität

The following efficacy-related outcomes were used as evidence to derive a recommendation: apnea-hypopnea index (the number of apnea or hypopnea events per hour), level of daytime sleepiness (Epworth Sleepiness Scale) and quality of life (Functional Outcomes of Sleep Questionnaire).

Domain safety

Sicherheit: Komplikationsraten

The following safety-related outcomes were used as evidence to derive a recommendation: serious adverse device effects (SADE), adverse events (AE) and serious adverse events (SAE).

Results

Available evidence

2 RCTs mit 67 T.
7 Ein-Arm-Studien mit 224 T.

We included randomised controlled trials for assessing efficacy and safety, in addition, prospective case-series with at least 10 patients and follow-up of 6 months for assessing safety.

In total, 2 RCTs with 67 participants and 7 single-arm studies with 224 patients met our inclusion criteria. Neither one of the RCTs reported on safety outcomes. The mean age of patients was 53-57 years in the RCTs, 50-55 years in the case series and the majority were males.

Clinical effectiveness

RCT 1: bei Therapierespondern Entzug der Therapie- Verschlechterung der Symptome

In responders to UAS treatment, selected from an uncontrolled single arm study, the withdrawal of therapy (control group) for 1 week resulted in statistically significant impairment of severity (AHI) of OSA, daytime sleepiness (ESS) and quality of life (FOSQ), which was considered clinically relevant compared to the intervention group (maintenance of therapy). After 6 months when therapy resumed, AHI, ESS and FOSQ showed no difference between groups.

RCT 2: Randomisierung HNS vs. Sham keine signifikanten Unterschiede nach 6 Mo

Another RCT randomised patients eligible for stimulation therapy with delayed therapy activation. After 6 months, AHI and ESS showed no statistically significant difference between the “device active” and the control group. Both groups showed a considerable reduction in AHI.

Safety

längste Studie 40 Mo
SADE in 2 %
469 AE in 126 P.

Serious device related adverse effects (SADE) occurred in 2% of patients and device explantation was performed in 2% of the patients at 40 months. Studies with smaller sample sizes showed higher rates of SADE and device explantation at 6 and 12 months.

The most recent and largest study reported 469 adverse events (AE) in 126 participants at 40 months, but the rate of both procedure and device related adverse events are reported to decrease over time after implantation.

Upcoming evidence

1 RCT registriert (Aura6000™)
1 RCT erwähnt (Inspire®)

Currently, there is one registered ongoing randomised controlled trial with an open-label, parallel assignment design for a four-month period with the Aura6000™ System (ImThera Medical Inc.).

Another randomised controlled trial with delayed therapy activation and 6-month follow-up is ongoing. Patient enrolment will be completed by 2016. The Inspire® UAS System (Inspire Medical, Inc.) will be implanted.

Discussion

Overall, the strength of evidence for efficacy and safety is low to very low. This is mainly due to one RCT with a withdrawal study design and the study design of single-arm studies.

2 RCTs

Both included RCTs are flawed due to small sample sizes and the inherent lack of blinding of hypoglossal nerve stimulation therapy. There is a high risk of bias in the withdrawal RCT associated with highly selected participants, not representative of the population affected by OSA.

1 RCT mit withdrawal design/ Randomisierung v. Therapierespondern: 1-wöchiger Entzug führt zu Verschlechterung der Symptome

As far as information was available, the other RCT used different inclusion criteria. The trial has been terminated after six months. The efficacy-related outcomes failed to show a significant between-group difference in the reduction of sleep apnea severity, owing to major unanticipated improvements in the control group. Both groups showed a considerable reduction in AHI, but the underlying cause of improvement of AHI in the control group is unknown.

1 RCT keine Unterschiede zwischen Interventions- und Kontrollgruppe: Studienabbruch

Although the strength of evidence for safety is very low, hypoglossal nerve stimulation for treatment of OSA does not seem to be related to lethal consequences but only to a high number of non-serious adverse events and less frequent serious adverse events.

In highly selected responders, the effects of withdrawal and resuming the therapy were attributable to hypoglossal nerve stimulation. However, the study design and the selection of responders do not allow assessing the relative effectiveness of the intervention. As responders do not represent the target population in this report, the study results cannot be used as evidence to derive a recommendation.

Effekt des Therapieentzugs nur in Therapierespondern gezeigt, sehr kurzer Zeitraum

Furthermore, it is known that a subset of eligible patients will respond to stimulation therapy anyway, but characteristics of responders and the extent to which the hypoglossal nerve stimulation is effective remain unknown. And, important information about the non-responders is lacking.

keine Informationen zu Gesamtzielgruppe; Anteil der Therapieresponder

The effect of stimulation therapy shown in responders was not reproducible in another study population eligible for stimulation therapy. The underlying cause of improvement of the severity of OSA independent of active stimulation remains unclear.

keine Kriterien zur PatientInnenauswahl

Long-term data regarding treatment effects, complications and compliance are lacking and none of the relevant clinical endpoints like cardiovascular morbidity or mortality were reported. Information on device durability beyond 40 months is lacking.

Langzeitdaten fehlen

Conclusion

The current evidence is not sufficient to prove that hypoglossal nerve stimulation for treating moderate-to-severe obstructive sleep apnea is more effective and equally safe compared to no treatment. New study results will potentially influence the effect estimate considerably. The implantation of UAS seems to be relatively safe and serious adverse events relatively rare.

Studienlage unzureichend um Wirksamkeit und Sicherheit abschließend zu beurteilen

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

obstruktive Schlafapnoe: schlafbezogene Atmungsstörung durch Kollaps der Rachenmuskulatur

Die obstruktive Schlafapnoe (OSA) ist eine schlafbezogene Atmungsstörung, bei der es während des Schlafes wiederholt zu einem Kollaps der Rachenmuskulatur kommt. Dadurch werden die oberen Atemwege teilweise oder komplett blockiert, es kommt zu Atempausen, intermittierender Hypoxämie und in Folge zu einer Weckreaktion des Körpers (Arousal). Begleitet werden die Atempausen häufig von lautem und unregelmäßigem Schnarchen. Zu den anatomischen Risikofaktoren gehören Adipositas mit einem BMI größer als 30, ein kurzer oder retrahierter Unterkiefer und laterale parapharyngeale Fettpolster. Der Verschluss der oberen Atemwege ist allerdings ein komplexer Vorgang, der von vielen Faktoren abhängig ist wie Alter, Gewicht und Geschlecht, Lebensstil, anatomische Besonderheiten im Rachenraum, genetische Ursachen, aber auch Veränderungen im Schlaf-Wach-Rhythmus.

Symptome: Tagesmüdigkeit, Atemaussetzer, Leistungsabfall, depressive Symptome

Die Symptome können übermäßige Tagesmüdigkeit, beobachtete Atemaussetzer, Leistungsabfall im Beruf und Alltag sowie depressive Symptome umfassen. Neben den damit verbundenen Risiken wie erhöhter Unfallgefahr im Straßenverkehr, birgt die obstruktive Schlafapnoe weitere erhebliche Risiken. Sie wird sehr häufig von einer arteriellen Hypertonie begleitet, das Herzinfarkt-, und Schlaganfall-Risiko steigt und es besteht eine erhöhte kardiovaskuläre Mortalität.

Apnoe-Hypopnoe-Index: Hinweis auf Schwere der OSA

Der Apnoe-Hypopnoe-Index (AHI) bezeichnet die durchschnittliche Anzahl von Apnoe- und Hypopnoe-Episoden pro Stunde Schlaf. Er ist ein Hinweis auf die Schwere einer schlafbezogenen Atmungsstörung. Es gibt allerdings keine einheitliche Einteilung des Schweregrads unter Verwendung des AHI. Laut der Amerikanischen Gesellschaft für Schlafmedizin (AASM) sowie nach der Medizinischen Leitlinie „Nicht erholsamer Schlaf – Schlafstörungen“ liegt ein leichtgradiges OSA bei einem AHI von 5-15 vor, ab einem AHI >15 und <30 wird die OSA als mittelgradig, und ab einem AHI >30 als schwer eingestuft [9, 10].

obstruktives Schlafapnoesyndrom (OSAS): AHI ≥5, Tagesschläfrigkeit

Etwa 2 bis 4 % der Erwachsenen leiden unter einem obstruktiven Schlafapnoe Syndrom (OSAS), das charakterisiert ist durch einen AHI ≥5 sowie Tagesschläfrigkeit. Die Prävalenz der symptomatischen OSA wird bei einem AHI größer als 15 mit 9 % bei Männern und 4 % bei Frauen angegeben.

Standardtherapie: CPAP

Die CPAP-Beatmung (kontinuierlicher positiver Atemwegsdruck) ist die gängige Schlafapnoe-Therapie bei einer mittel-bis-schwergradigen obstruktiven Schlafapnoe. CPAP wird über eine Nasenmaske (Schlafapnoe-Maske) appliziert und stabilisiert durch einen leichten Überdruck über den gesamten Atemzyklus die oberen Luftwege – vom Naseneingang bis zur Luftröhre.

CPAP: geringe Compliance

International wird die Compliance mit der CPAP Therapie mit 40-60 % angegeben. Dabei nutzen 29-83 % der OSA PatientInnen die Therapie regelmäßig weniger als 4 Stunden [9]. Daher bleibt ein Teil der Schlaf-Apnoe PatientInnen unzureichend behandelt, wenn man nur die Therapie mit CPAP betrachtet. Neben anderen Behandlungsmethoden wie Unterkieferprotrusionsschiene, Gewichtsreduktion, Änderung der Schlafposition mit Vermeidung der Rückenlage, durch ein Lagetraining oder über Hilfsmittel wie Schlafwesten, kann in seltenen ausgewählten Fällen auch eine Operation an den oberen Atemwegen in Erwägung gezogen werden.

Therapieziel: Normalisierung des AHI, Reduktion von Krankheitsrisiko und Sterblichkeit

Das kurzfristige Therapieziel bei einer OSA besteht in der Reduktion von hypoxischen Episoden und Schlaffragmentierung sowie einer Reduktion bzw. Normalisierung des AHI, das längerfristige Ziel ist die Reduktion des mit OSA einhergehenden erhöhten Risikos für Herz-Kreislauf-Erkrankungen und der erhöhten Sterblichkeitsrate.

Beschreibung der Technologie

elektrische Stimulation des Nervus hypoglossus – Tonisierung des Atemwegsöffners M.genioglossus

Eine Mehrzahl von Faktoren sind an der Pathogenese der OSA beteiligt, neben Übergewicht als wesentlicher Kofaktor ist ein herabgesetzter Tonus der Muskulatur, die für das Offenhalten der oberen Atemwege im Schlaf verantwortlich ist, entscheidend. Ein neuer, funktioneller Therapieansatz bei OSA besteht in der elektrischen Stimulation des Nervus hypoglossus während des Schlafes, da dieser den wesentlichen Atemwegsöffner, den Musculus genioglossus innerviert. Auf diesem Weg soll die insuffiziente Tonisierung der am Offenhalten der Atemwege beteiligten Muskulatur während des Schlafes durch ein implantierbares System wiederhergestellt werden [6-8]. Die direkte Muskelstimulation des M. genioglossus durch intramuskuläre oder transkutane Elektroden hat sich als nicht erfolgreich herausgestellt, da diese Stimulation zu Schlafunterbrechungen geführt hat [11-13].

drei CE-zertifizierte Systeme, eines nicht mehr am Markt

Es wurden drei Systeme zur Stimulation des Nervus hypoglossus unterschiedlicher Hersteller in klinischen Studien überprüft, die alle ein CE-Zertifikat haben.

- Inspire® Upper Airway Stimulation (UAS) System (Inspire Medical Systems, Inc.)
- Aura6000™ System (ImThera Medical, Inc.)

Das dritte Produkt ist allerdings nicht mehr verfügbar

- HNS/HGNS® System (Apnex Medical, Inc.)

subkutane Implantation des Generators und Stimulation des Nervs durch Elektrode

unterschiedliche Atmungssensorsysteme

Allen drei Systemen gemeinsam ist die einseitige subkutane Implantation einer Nervenstimulatoreinheit und die direkte Stimulation des N. hypoglossus durch eine anliegende Stimulationselektrode. Zwei dieser Systeme stimulieren den Nervus hypoglossus atmungssynchron. Die Differenzierung zwischen Inspiration und Exspiration wird durch einen interkostal liegenden Drucksensor bei Inspire® UAS (Inspire Medical Inc.) bzw. durch einen subkutan liegenden Impedanzsensor bei HNS/HGNS® (Apnex Medical, Inc.) erreicht. Bei dem dritten System (Aura6000TM ImThera Medical Inc.) erfolgt die Stimulation nicht in Abhängigkeit zur Atmung, sondern kontinuierlich, indem alternierend unterschiedliche Faserbündel des Nerven stimuliert werden und andere nicht, dadurch kommt es zu einer sich ständig verändernden aber nie verschwindenden Tonisierung der Zunge.

Zielgruppe: OSA PatientInnen, Zweitlinientherapie nach CPAP

Alle Systeme sind für PatientInnen mit OSA gedacht, die eine CPAP-Therapie nicht vertragen bzw. damit nicht erfolgreich zu behandeln sind. Einen Monat nach Implantation werden sie erstmals aktiviert, grob orientierend im Wachzustand eingestellt und im Schlaflabor schließlich feineingestellt.

In den USA hat das Inspire® Upper Airway Stimulation (UAS) System eine Zulassung der FDA für eine Untergruppe von PatientInnen mit einer mittel-bis-schwergradigen obstruktiven Schlafapnoe mit AHI zwischen 20 und 65 und ohne anatomische Auffälligkeiten, die als Ursache der OSA in Frage kommen.

Das HNS/HGNS® System (Apnex Medical, Inc.) hat keine FDA Zulassung und das Aura6000™ System (ImThera Medical, Inc.) hat eine Forschungsausnahmegenehmigung der FDA für eine laufende Studie (NCT02263859).

Ein weiteres Produkt ist ein Implantat in klinischer Prüfung und weder in Europa noch in den USA erhältlich und hat eine Forschungsausnahmegenehmigung der FDA für die klinische Studie NCT02312479.

- Nyxoah SAT System (Nyxoah)

Nyxoah ist ein sehr kleines und minimalinvasives Gerät zur Neurostimulation. Es wird mittels eines kleinen Einschnitts nahe den Nerven des Zungenmuskels implantiert.

HNS wirksamer und zumindest gleich sicher als keine Intervention?

Der Bericht behandelt die Frage, ob die Behandlung von mittel-bis-schwergradiger obstruktiver Schlafapnoe mittels elektrischer Stimulation des Nervus hypoglossus wirksamer und zumindest genauso sicher wie „keine Intervention" ist.

Vergleich in den Studien: sham Intervention

Keine Intervention meint in diesem Zusammenhang, dass das Stimulationssystem implantiert, aber nicht aktiviert wird. Ein Vergleich mit CPAP Therapie ist deshalb nicht möglich, weil nur PatientInnen, die keine CPAP Therapie tolerieren oder akzeptieren für eine Therapie mittels Stimulation des Nervus hypoglossus in Frage kommen. Die Aktivierung des Stimulationssystems erfolgt in einer Schlafnacht im Schlaflabor (Titrationsnacht). Die Stimulation wird vom/von der Patienten/in vor dem Schlafengehen und nach dem Aufwachen mittels einer Fernbedienung aktiviert bzw. deaktiviert. Daher war weder eine Verblindung des behandelten Arztes noch der PatientInnen in den Studien möglich. Um diesem potentiellen Informationsbias entgegenzuwirken, könnte eine subtherapeutische Stimulation als „Scheinbehandlung" in Erwägung gezogen werden [14].

Methoden

systematischer Literaturreview

Die Beantwortung der Forschungsfragen bezüglich Wirksamkeit und Sicherheit erfolgte anhand einer systematischen Literatursuche in folgenden Datenbanken:

- Medline via Ovid,
- Embase,
- the Cochrane Library,
- CRD (DARE, NHS-EED, HTA)

Zusätzlich wurde noch eine Handsuche durchgeführt und es gab eine Anfrage nach Studien bei den einzelnen Herstellern. Die Studienauswahl erfolgte unabhängig durch beide Autoren (ISF, AK). Der Erstautor (ISF) extrahierte die Studiendaten und die Zweitautorin (AK) kontrollierte die Daten.

Die Daten der für die Entscheidung herangezogenen Endpunkte wurden aus den einzelnen Studien zusammengefasst und nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet.

Zusätzlich wurde das Bias-Risiko der Studien durch die Erstautorin (ISF) bewertet und die Daten von der Zweitautorin (AK) kontrolliert.

Klinische Wirksamkeit

Wirksamkeit: Schweregrad der OSA Tagesschläfrigkeit Lebensqualität

Zur Bewertung der Wirksamkeit der Stimulation des Nervus hypoglossus wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

- Schweregrad der obstruktiven Schlafapnoe (AHI)
- Tagesschläfrigkeit (Epworth Sleepiness Scale)
- Lebensqualität (Functional Outcomes of Sleep Questionnaire)

Kardiovaskuläre Morbidität und Mortalität sind wichtige klinische Endpunkte, wurden aber aufgrund der frühen Entwicklungsphase der Stimulation des Nervus hypoglossus nicht in diesem Bericht berücksichtigt.

Sicherheit

Sicherheit: Komplikationsraten

Zur Bewertung der Sicherheit der Stimulation des Nervus hypoglossus wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

- schwere unerwünschte produktbezogene Ereignisse (SADE)
- unerwünschte Ereignisse (AE)
- schwere unerwünschte Ereignisse (SAE)

Ergebnisse

Verfügbare Evidenz

2 RCTS mit 67 T. 7 Ein-Arm-Studien mit 224 T.

Es wurden randomisierte kontrollierte Studien (RCTs) zur Bewertung der Wirksamkeit und Sicherheit eingeschlossen, die eine Behandlung einer mittel-bis-schwergradigen obstruktiven Schlafapnoe mittels Stimulation des Nervus hypoglossus mit „keiner Intervention“ verglichen. Zusätzlich wurden unkontrollierte Beobachtungsstudien (sogenannte Ein-Arm-Studien) mit 10 oder mehr PatientInnen zur Bewertung der Sicherheit eingeschlossen.

2 RCTs mit 67 StudienteilnehmerInnen und 7 Ein-Arm-Studien mit 224 StudienteilnehmerInnen entsprachen den Einschlusskriterien. Beide RCTs berichteten keine Ergebnisse zur Sicherheit.

Durchschnittsalter 53–57 J. mittel- bis schwergradige Schlafapnoe

Das Durchschnittsalter der PatientInnen lag zwischen 53 und 57 Jahren in den RCTs und zwischen 50 und 55 in den unkontrollierten Beobachtungsstudien mit einem ganz überwiegenden Anteil von Männern. Die Nachbetrachtungszeit der meisten Studien lag bei 6 und 12 Monaten, wobei es auch eine Studie mit 40 Monaten (entspricht 3 Jahren und 4 Monaten) Nachbetrachtungszeit gab. Die Studien untersuchten die Behandlung von mittelbis schwergradiger obstruktiver Schlafapnoe, wobei sich die Einschlusskriterien hinsichtlich des Schweregrads gemessen anhand des AHI sowie des Body-Maß-Index (BMI) geringfügig unterschieden. Einer der beiden RCTs exkludierte PatientInnen mit einem vollständigen konzentrischen retropalatalen Kollaps in einer vorangegangenen medikamentös induzierten Schlafendoskopie.

In einem der beiden RCTs wurde das Inspire® Upper Airway Stimulation (UAS) System, in dem anderen RCT das HNS/HGNS® System implantiert.

Klinische Wirksamkeit

RCT 1: Randomisierung von Therapierespondern auf Beibehaltung oder 1-wöchigem Absetzen der Therapie

Anstieg des AHI und Verschlechterung der ESS, FOSQ nach Absetzen

Therapieresponder, die nach 12 Monaten Beobachtungszeit in einer unkontrollierten Beobachtungsstudie konsekutiv ausgewählt wurden, wurden einer 7-tägigen randomisierten kontrollierten Therapieentzugsphase unterzogen. Das Ansprechen auf die Therapie wurde vorab definiert als Reduktion des AHI um 50 % des Ausgangswertes und AHI kleiner als 20. In der Therapieentzugsgruppe (Kontrollgruppe) kam es zu einem signifikanten Anstieg des AHI und zu einer signifikanten Verschlechterung der Tagesschläfrigkeit (ESS) und der Lebensqualität (FOSQ), die auch klinisch relevant waren. In der Therapieerhaltungsgruppe (Interventionsgruppe) gab es keine Änderung der Werte. Nach 1 Woche wurde die Therapie in der Therapieentzugsgruppe wieder fortgesetzt und nach 6 Monaten zeigten sich keine Unterschiede zwischen beiden Gruppen bei den Endpunkten AHI, ESS und FOSQ.

RCT2: Randomisierung HNS vs. Sham keine signifikanten Unterschiede nach 6 Mo

Der zweite RCT randomisierte PatientInnen in eine Kontrollgruppe mit Implantation ohne Aktivierung des Neurostimulators und eine Interventionsgruppe mit Aktivierung. Das Ansprechen auf die Therapie wurde vorab definiert als Reduktion des AHI um 50 % des Ausgangswertes und AHI kleiner als 20. Nach 6 Monaten zeigte sich kein statistisch signifikanter Unterschied des AHI und der Tagesschläfrigkeit (ESS) zwischen beiden Gruppen.

Sicherheit

längste Studie 40 Mo
SADE in 2 %
469 AE in 126 P.

Schwere unerwünschte produktbezogene Ereignisse (SADE) traten in 2 % der PatientInnen auf, eine Explantation erfolgte ebenfalls in 2 % in einem Beobachtungszeitraum von 40 Monaten. Studien mit kleinen Fallzahlen zeigten höhere Raten an schweren unerwünschten produktbezogenen Ereignissen und Explantationen in einem Beobachtungszeitraum von 6 bzw. 12 Monaten.

Unerwünschte Ereignisse (AE) wie Schmerzhaftigkeit, vorübergehende Schwäche der Zunge, Unbehagen aufgrund der elektrischen Stimulation waren häufig, 469 Ereignisse traten in 126 PatientInnen in einem Beobachtungszeitraum von 40 Monaten auf.

Laufende Studien

1 RCT registriert (Aura6000™)

Aktuell ist eine laufende randomisierte kontrollierte Studie registriert (NCT02263859). Die kontrollierte Studie läuft 4 Monate, danach wird der Neurostimulator auch in der Kontrollgruppe aktiviert. Die zweite Phase der Studie läuft weitere 8 Monate. In der Studie wird das Aura6000™ System (ImThera Medical Inc.) implantiert. Erste Fertigstellung ist Mai 2016.

1 RCT erwähnt (Inspire®)

Eine weitere randomisierte kontrollierte Studie mit einer verzögerten Aktivierung der Stimulationstherapie wird in den Unterlagen des Dossiers eines Herstellers erwähnt. Der Beobachtungszeitraum ist 6 Monate, die laufende Rekrutierung von 40 PatientInnen wird im Jahr 2016 abgeschlossen sein. Die Studie wurde nicht in den aufgesuchten Registern und Datenbanken für klinische Studien gefunden.[1] In der Studie wird das Inspire® UAS System (Inspire Medical Systems, Inc.) implantiert.

[1] ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials (EUdraCT)

Diskussion

2 RCTs

Ziel des Berichts war es die Wirksamkeit und Sicherheit der Stimulation des Nervus hypoglossus bei der Behandlung der mittel-bis-schwergradigen obstruktiven Schlafapnoe im Vergleich zu keiner Intervention zu untersuchen.

Zwei RCTs wurden für die Bewertung der Wirksamkeit herangezogen. Sieben unkontrollierte Beobachtungsstudien wurden für die Bewertung der Sicherheit herangezogen, da keine der beiden RCTs Ergebnisse zur Sicherheit berichteten.

1 RCT mit withdrawal design/ Randomisierung v. Therapierespondern: 1-wöchiger Entzug führt zu Verschlechterung der Symptome

Insgesamt inkludierten beide RCTs [14, 15] 67 PatientInnen mit mittel-bis-schwergradiger obstruktiver Schlafapnoe, allerdings unterschieden sich die Inklusionskriterien, soweit diese Information für den RCT, der nur als Abstract publiziert wurde, verfügbar war. In beiden Studien wurde das Ansprechen auf die Therapie vorab definiert, als Reduktion des AHI um 50 % des Ausgangswertes und AHI kleiner als 20.

Ein RCT hatte ein „withdrawal design" [14]. Nach 12 Monaten Beobachtungszeit in einer prospektiven unkontrollierten Beobachtungsstudie [16] wurden die ersten 46 konsekutiven PatientInnen, die ein Ansprechen auf die Stimulationstherapie (Therapieresponder) zeigten, entweder in die Therapieentzugsgruppe (Kontrollgruppe) oder in die Therapieerhaltungsgruppe (Interventionsgruppe) randomisiert. Die Therapieentzugsphase dauerte 1 Woche, danach wurde in beiden Gruppen die Stimulationstherapie für weiter 6 Monate fortgesetzt.

Die für die unkontrollierte Studie vorab definierten Ein-und Ausschlusskriterien erlaubten keinen Einschluss von PatientInnen mit einem vollständigen konzentrischen retropalatalen Kollaps, der in einer medikamentös induzierten Schlafendoskopie ausgeschlossen wurde. Daher trifft dieses Ausschlusskriterium auch für die selektierte randomisierte Subgruppe der unkontrollierten Studie zu. Es ist aber unklar, ob ein solches Ausschlusskriterium auch in dem zweiten RCT zur Anwendung gekommen ist, da nur auf Angaben des publizierten Abstracts mit Studienergebnissen von 21 PatientInnen und der Datenbank des klinischen Studienregisters[2] zurückgegriffen werden konnte.

1 RCT keine Unterschiede zwischen Interventions- und Kontrollgruppe: Studienabbruch

Der zweite RCT [15] wurde vorzeitig nach einer negativen Interimsanalyse nach 6 Monaten beendet. Sowohl PatientInnen der Interventionsgruppe als auch der Kontrollgruppe wurde das HNS/HGNS® System (Apnex Medical, Inc.) implantiert. In der Interventionsgruppe wurde ein Monat nach der Implantation die Stimulation aktiviert, in der Kontrollgruppe hätte die Aktvierung 7 Monate nach der Implantation stattfinden sollen. Im Rahmen der Interimsanalyse nach 6 Monaten zeigten sich keine statistisch signifikanten Gruppenunterschiede betreffend Schweregrad gemessen anhand des AHI und der Tagesschläfrigkeit anhand des ESS aufgrund nicht erwarteter Verbesserungen in der Kontrollgruppe. Beide Gruppen hatten eine deutliche Reduktion des AHI, aber die zugrundeliegende Ursache der Verbesserung in der Kontrollgruppe bleibt unklar.

Der einwöchige Therapieentzug in der RCT Subgruppe [14] führte zu einer Verschlechterung aller Ergebnisse betreffend die Wirksamkeit. Nach Wiederaufnahme der Therapie fanden sich nach 6 Monaten keine Gruppenunterschiede.

[2] https://clinicaltrials.gov/ct2/show/record/NCT01446601

kleine Fallzahlen, fehlende Verblindung

Kritikpunkte der beiden Studien sind vor allem die kleinen Fallzahlen und die der Intervention inhärente Unmöglichkeit der Verblindung von PatientInnen und behandelten ÄrztInnen. Es besteht ein hohes Bias-Risiko in dem RCT, da aus einer unkontrollierten Beobachtungsstudie eine Subgruppe von Therapierespondern ausgewählt wurde, die nicht repräsentativ sind für die Population mit einer mittel-bis schwergradigen OSA. Weiters erlaubt eine 7 tägige Therapieentzugsphase keine Beurteilung einer Effektivität über einen längeren Zeitraum.

Effekt des Therapieentzugs nur in Therapierespondern gezeigt, sehr kurzer Zeitraum

Die in der Studie gezeigten Effekte des Therapieentzugs und der Wiederaufnahme der Therapie in einer hochselektierten PatientInnengruppe, nämlich nachgewiesenen Therapierespondern, sind auf die Intervention zurückzuführen. Das Studiendesign und die Selektion von Therapierespondern erlaubt damit allerdings keine Beurteilung der relativen Effektivität. Da Therapieresponder nicht die Zielgruppe des Berichts sind, können diese Studienergebnisse nicht als Evidenz für eine Empfehlung herangezogen werden.

keine Informationen zu Gesamtzielgruppe; Anteil der Therapieresponder

Weiters ist bekannt, dass bestimmte PatientInnen auf die Stimulationstherapie ansprechen, aber es bleibt unklar, wer diese Responder sind, wieviele auf die Therapie ansprechen und wie wirksam die Therapie tatsächlich ist. Informationen zu den Nicht-Respondern fehlen ebenfalls.

Der Effekt der Stimulationstherapie, der bei Respondern gezeigt wurde, war in einer anderen Studienpopulation, randomisiert in eine Kontrollgruppe ohne Aktivierung der Stimulation und in eine Behandlungsgruppe mit Aktvierung, nicht nachweisbar. Die zugrundeliegende Ursache für die Verbesserung des Schweregrades der OSA, unabhängig von der Aktivierung der Stimulation bleibt unklar.

keine Kriterien zur PatientInnenauswahl

Die richtige PatientInnenauswahl dürfte essentiell für den Erfolg der Behandlung sein, aber exakte Kriterien für die PatientInnenauswahl fehlen, weil PatientInnencharakteristika von Therapierespondern nur ungenügend bekannt sind. Die vorliegenden Daten legen nahe, dass eine inkorrekte PatientInnenauswahl eine große Limitation darstellen könnte.

Insgesamt sieben Publikationen von 4 Fallserien entsprachen den Einschlusskriterien zur Beurteilung der Sicherheit [16-21].

2 % SADE
2 % Explantationen innerhalb 40Mo

Schwere unerwünschte produktbezogene Ereignisse (SADE), wie Wundinfektionen, Elektrodenbrüche und Repositionierung des Neurostimulators traten in 2 % der PatientInnen auf, eine Explantation erfolgte in 2 % der Fälle in einem Beobachtungszeitraum von 40 Monaten. Studien mit kleinen Fallzahlen zeigten höhere Raten an schweren unerwünschten produktbezogenen Ereignissen und Explantationsraten bis 13 % in einem Beobachtungszeitraum von 6 bzw. 12 Monaten. Todesfälle, die auf die Intervention zurückzuführen waren, sind nicht aufgetreten.

469 AE in 126 P. nach 40 Mo

Unerwünschte Ereignisse (AE), wie Schmerzhaftigkeit, Läsionen und vorübergehende Schwäche der Zunge, sowie Unbehagen aufgrund der elektrischen Stimulation waren häufig, 469 Ereignisse traten in 126 PatientInnen in einem Beobachtungszeitraum von 40 Monaten auf.

Insgesamt ist die Stärke der Evidenz für die Effektivität und Sicherheit der Stimulation des Nervus hypoglossus im Vergleich zu keiner Behandlung als niedrig bis sehr niedrig einzuschätzen. Schwere unerwünschte produktbezogene Ereignisse (SADE) traten relativ selten auf. Langzeitdaten zu Wirksamkeit, Komplikationen und Compliance der PatientInnen fehlen, ebenso

zu kardiovaskulären Erkrankungen und Mortalität als relevante Endpunkte bei OSA.

2 laufende RCT

Aktuell ist eine laufende randomisierte kontrollierte Studie registriert (NCT02263859). In der Studie wird das Aura6000™ System (ImThera Medical, Inc.) implantiert. Eine weitere randomisierte kontrollierte Studie mit einer verzögerten Aktivierung der Stimulationstherapie ist im Laufen, die Rekrutierung von 40 PatientInnen wird im Jahr 2016 abgeschlossen sein. In der Studie wird das Inspire® UAS System (Inspire Medical Systems, Inc.) implantiert.

Die entscheidende Schwäche des vorliegenden Berichts liegt in der Unvollständigkeit der verfügbaren Informationen über die Studie, die vom Unternehmen vorzeitig nach einer negativen Interimsanalyse beendet wurde. Trotzdem entschieden wir den RCT zu inkludieren um ein selektives Berichten zu verhindern. Allerdings war es nicht möglich anhand der im Abstract angegebenen Informationen das Bias-Risiko zu beurteilen. Inwieweit das eine Änderung in der Einschätzung ergeben hätte, ist unklar, die Möglichkeit wird aber als gering erachtet.

Empfehlung

Studienlage unzureichend um Wirksamkeit und Sicherheit abschließend zu beurteilen

Die gegenwärtige Studienlage lässt keine Rückschlüsse zu, ob eine Behandlung der mittel-bis schwergradigen OSA mittels Stimulation des Nervus hypoglossus wirksamer oder gleich sicher ist als die Vergleichsintervention „keine Behandlung“.

Re-evaluierung für 2018 empfohlen

Neue Studien werden möglicherweise einen wichtigen Einfluss auf die Einschätzung des Effekts haben. Eine neuerliche Evaluierung wird im Jahr 2018 vorgeschlagen, da Ergebnisse aus neuen RCTs vorliegen werden. Die Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen.

1 Scope

1.1 PICO question

PIKO-Frage

Is hypoglossal cranial nerve stimulation in comparison to no treatment in adult patients with moderate-to-severe obstructive sleep apnea, who do not accept or have failed to comply with CPAP treatment, effective and safe concerning reduction in OSA severity, daytime sleepiness, quality of life and serious adverse events?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized 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 First/second line treatment
Intervention	Hypoglossal cranial nerve stimulation (HNS) ["Electric Stimulation Therapy"]
Control	No stimulation treatment[3]
Outcomes	
Efficacy	Severity of obstructive sleep apnea (Apnea- hypopnea index; the number of apnea and hypopnea events per hour of sleep) Level of daytime sleepiness (e.g. Epworth Sleepiness Scale) Quality of life
Safety	Serious adverse device effect (SADE) Serious adverse events (SAE) Adverse events (AE)
Study design	
Efficacy	Randomised controlled trials
Safety	Randomised controlled trials Prospective case-series [with at least 10 patients, length of follow-up at least 6 months] Registries with more than 100 patients

[3] Although CPAP therapy is the first line therapy in moderate-to-severe obstructive sleep apnea, a control group of therapeutic CPAP users is impractical because only patients who could not use CPAP, or who declined to do so, are the target group of the intervention.

2 Methods

2.1 Research questions

Description of the technology	
Element ID	Research question
B0001	What is hypoglossal nerve stimulation and the comparator(s)?
A0020	For which indications has hypoglossal nerve stimulation received marketing authorisation or CE marking?
B0002	What is the claimed benefit of hypoglossal nerve stimulation in relation to the comparator(s)?
B0003	What is the phase of development and implementation of hypoglossal nerve stimulation and the comparator(s)?
B0004	Who administers hypoglossal nerve stimulation and in what context and level of care is it provided?
B0008	What kind of special premises are needed to use hypoglossal nerve stimulation?
B0009	What supplies are needed to use hypoglossal nerve stimulation?
A0021	What is the reimbursement status of hypoglossal nerve stimulation?

Health problem and Current Use	
Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for OSA?
A0004	What is the natural course of OSA?
A0005	What are the symptoms and the burden of OSA for the patients?
A0006	What are the consequences of OSA for the society?
A0024	How is OSA currently diagnosed according to published guidelines and in practice?
A0025	How is the OSA condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is hypoglossal nerve stimulation utilised?

Clinical Effectiveness	
Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0005	How does hypoglossal nerve stimulation affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does hypoglossal nerve stimulation affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of hypoglossal nerve stimulation on patients' body functions?
D0016	How does the use of hypoglossal nerve stimulation affect activities of daily living?
D0012	What is the effect of hypoglossal nerve stimulation on generic health-related quality of life?
D0013	What is the effect of hypoglossal nerve stimulation on disease-specific quality of life?
D0017	Were patients satisfied with hypoglossal nerve stimulation?

Safety	
Element ID	Research question
C0008	How safe is hypoglossal nerve stimulation in comparison to the comparator(s)?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of hypoglossal nerve stimulation?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of hypoglossal nerve stimulation?

2.2 Sources

Description of the technology

Quellen

- Systematic literature search in Medline via Ovid, Embase, the Cochrane Library plus CRD (DARE, NHS-EED, HTA): see Section 2.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospitals
- Handsearch for guidelines

Health problem and Current Use

- Systematic literature search in Medline via Ovid, Embase, the Cochrane Library plus CRD (DARE, NHS-EED, HTA): see Section 2.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospitals
- Handsearch for guidelines

2.3 Systematic literature search

systematische Literatursuche in vier Datenbanken

The systematic literature search was conducted on the 18th and 21st of December 2015 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

The systematic search was limited to clinical trials in Medline and Embase. After deduplication, overall 180 citations were included. The specific search strategy employed can be found in the appendix.

Manufacturers from two products (Inspire Medical Systems, Inc., ImThera Medical Inc.) submitted 21 publications of which 1 new citation was identified. By hand-search (Scopus), an additional 22 were found, resulting in overall 223 hits.

insgesamt 223 Publikationen identifiziert

2.4 Flow chart of study selection

Literaturauswahl

Overall 223 hits were identified. The references were screened by two independent researchers (ISF, AK) and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1. Articles that were excluded due to several reasons but still used as background are categorised under "background literature". Furthermore, we were not able to order 1 article, categorised under "not available".

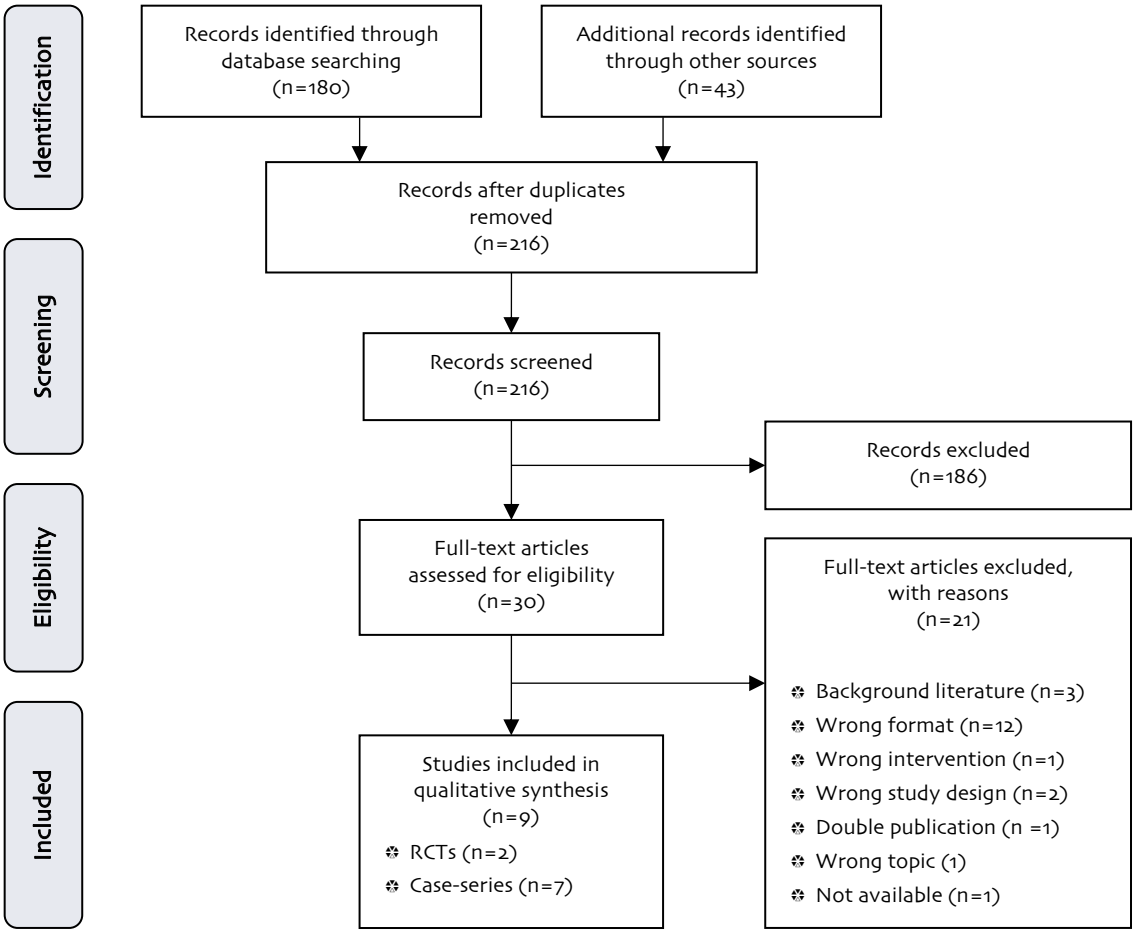

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

keine weiteren Datenanalysen, Biasrisiko analyse

The relevant information from the feasible studies was retrieved without any further analysis. For all studies the methodological quality was assessed by two independent researchers (ISF, AK) using a standardized risk of bias assessment tool [22] and a checklist for case series [23]. The risk of bias analysis for each individual study is shown in the Appendix (Chapter "Risk of bias tables") (see Table A-3, Table A-4).

2.6 Synthesis

qualitative Synthese, GRADE

The questions were answered in plain text format. In addition, evidence tables are used to show relevant information on the individual studies. Based on the evidence tables, data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [24] Table 7-1.

The analysis of efficacy data is qualitative and not quantitative due to heterogeneity of the data. The analysis of safety related data is qualitative and not quantitative due to lack of comparison groups since RCTs did not report safety data.

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is hypoglossal nerve stimulation and the comparator(s)?

elektrische Stimulation des Nervus hypoglossus – Tonisierung des Atemwegsöffners M.genioglossus

A number of factors contribute to OSA pathogenesis, including decreased tone during sleep in the upper airway dilator muscles, e.g. the genioglossus [5]. This notion has led to investigations of electrical stimulation of genioglossus using intramuscular or transcutaneous electrodes. But muscle stimulation led to disrupted sleep because of sensory phenomena [11-13]. As a result, direct electrical stimulation of the motor nerve innervating the genioglossus muscle, the hypoglossal nerve (HGN), has been explored as an alternative [6-8]. Hypoglossal nerve stimulation involves a surgical procedure for device implantation. Stimulation of the HGN causes contraction of both the retrusor (styloglossus and hyoglossus) and the protrusor (genioglossus) muscles of the tongue thus maintaining an open airway during sleep.

drei CE-zertifizierte Systeme, eines nicht mehr am Markt

Currently, two products of hypoglossal nerve stimulation implants are marketed by two manufacturers

- Inspire® Upper Airway Stimulation (UAS) System (Inspire Medical Systems, Inc.)
- Aura6000™ System (ImThera Medical, Inc.)

A third product is not available anymore

- HNS/HGNS® System (Apnex Medical, Inc.)

A fourth product is an investigational device, not for sale in Europe or US

- Nyxoah SAT System (Nyxoah)

Technical description of HGNS Systems

subkutane Implantation des Generators und Stimulation des Nervs durch Elektrode

unterschiedliche Atmungssensorsysteme

- Inspire® Upper Airway Stimulation (UAS) therapy consists of a breathing sensor and a stimulation lead, powered by a small battery, which are both implanted. The breathing sensor is a pulmonary pressure sensor to sense respiration. The neurostimulator delivers electrical stimulating pulses to the hypoglossal nerve through the stimulation lead; the stimulating pulses are synchronised with ventilation detected by the sensing lead. The system delivers mild stimulation to key airway muscles.
- Aura6000TM System (ImThera Medical, Inc.) consists of an implanted pulse generator (IPG), a small implant containing the battery and stimulation system, and a multi-electrode lead with a silicone cuff housing six independent electrodes connected to the IPG. The six stimulating electrodes are radially in contact with the cylindrical body of the proximal hypoglossal nerve. The device stimulates multiple muscles of the tongue compared with the other devices, which only stimulate the largest muscle.
- HNS/HGNS® System (Apnex Medical, Inc.) senses respiration using two leads. A nerve cuff electrode on the distal end of the stimulation lead is implanted on a branch of the hypoglossal nerve in the submandibular region. The proximal end of the stimulation lead is tunneled under the skin to the Neurostimulator. The respiration sensing

leads are tunneled under the skin from the neurostimulator to the costal margins. Stimulation is generated by the neurostimulator, synchronised with inspiration as measured by the respiration sensing leads using bio-impedance, and delivered to the hypoglossal nerve by the stimulation lead.

Inspire® UAS and HNS/HGNS® Systems are technically similar in that both systems sense respiration. Aura6000TM Systems, unlike Inspire® UAS and HNS/HGNS® Systems do not have a mechanism to sense respiration.

Table 3-1: Technical components of hypoglossal nerve stimulation systems

	Inspire® Upper Airway Stimulation (Inspire Medical, Inc.)	Aura6000TM System (ImThera Medical, Inc.)	HNS/HGNS® System (Apnex Medical, Inc.)
Implanted pulse generator (neurostimulator)	Right ipsilateral mid-infraclavicular region	upper chest rechargeable battery recharging performed transcutaneously with external remote control charger	Right ipsilateral mid-infraclavicular region
Stimulation lead	Synchronised with ventilation cuff section with 3 electrodes	multi-electrode lead 6 independent electrodes	Synchronised with inspiration detected by respiration sensing leads
Respiration sensing lead	Sensing side facing the pleura pulmonary pressure sensor	-	2 leads detect inspiration using bio-impedance

Common to all, a small handheld sleep remote is used by patients to turn stimulation therapy on at night before going to bed and off in the morning after waking up. The remote control charger to charge the battery in the Aura6000TM System is also used to start and end each night session of stimulation.

Nyxoah is an ultra-small Neurostimulator that measure 20mm in diameter and is 2.5mm thick. It's designed to be implanted close to the nerves of the tongue muscle by a single small incision. A fundamental difference to other neurostimulation devices is that the Nyxoah SAT System can monitor the tongue and stimulate the muscles only when it blocks the airway.[4] The FDA has approved an investigational device exemption (IDE) for the clinical study NCT02312479.

Komparator: keine Behandlung, da nur für therapierefraktäre PatientInnen

Verblindung schwierig

The comparator is 'no treatment' because only those patients who could not use CPAP, or who declined to do so, are the target group of the intervention. 'No treatment' means that the device is implanted but not activated. Blinding of patients was impossible because they have to turn simulation therapy on at night. Blinding of treating physicians was impossible as well. The stimulation settings were adjusted in an overnight sleep study, so called titration night, after a healing period of approximately 30 days after implantation. To potentially reduce information bias, subtherapeutic stimulation as sham treatment could be taken into consideration [14].

[4] http://www.nyxoah.com/product, accessed 26022016

A0020 – For which indications has hypoglossal nerve stimulation received marketing authorisation or CE marking?

Indikationen: mittel- bis schwergradige OSA; Zweitlinientherapie nach CPAP

Inspire® Upper Airway Stimulation (UAS) therapy has received CE Mark approval in 2010 for the treatment of a subset of patients with moderate-to-severe OSA. One contraindication for use is an unresolved complete concentric collapse at the level of the soft palate.[5]

In the US, FDA approved the device in 2014 to treat a subset of patients with moderate-to-severe OSA, AHI ≥20 and ≤65 in adult patients of 22 years of age and older who have been confirmed to fail or cannot tolerate Positive Airway Pressure (PAP) treatments and who do not have a complete concentric collapse at the soft palate level.[6]

The Aura6000TM System has received the European CE Mark approval in 2012 for the treatment of OSA.[7]

In 2014, FDA has approved an investigational device exemption (IDE) for the Aura6000TM System for the clinical study NCT02263859. Data from this pivotal clinical study will be used to support a Pre-Market Approval (PMA) application.[8]

Apnex Medical, Inc. has received CE Mark approval for its HNS/HGNS® System in 2011 for use by people who suffer from obstructive sleep apnea. The system was approved for sale in Europe. Apnex Medical, Inc. received investigational device exemption (IDE) approval from the U.S. FDA to conduct a clinical study.[9] Apnex Medical, Inc. officially ceased operations in March 2013 because of an unsuccessful clinical trial.[10]

B0002 – What is the claimed benefit of hypoglossal nerve stimulation?

erwarteter Nutzen: Reduktion der OSA, verbesserte Schlaf- und Lebensqualität

The expected main benefit is a significant reduction in obstructive sleep apnea as well as improvements in the quality of sleep and quality of life in OSA patients not accepting or tolerating CPAP.

The benefit in overall health, cardiovascular morbidity and mortality needs to be scientifically confirmed in the long-term.

B0003 – What is the phase of development and implementation of hypoglossal nerve stimulation?

klinische Prüfung

Clinical trials using hypoglossal nerve stimulation have been undertaken, clinical trial sites in Austria did not participate.

---

5 Information from the dossier of Inspire provided for evaluation at LBI-HTA.

6 http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130008a.pdf (accessed 03032016)

7 http://imtheramedical.com/blog/2012/03/14/imthera-medical-announces-european-ce-mark-approval-for-the-aura6000-system-to-treat-obstructive-sleep-apnea/ (accessed 03032016)

8 http://imtheramedical.com/blog/2014/11/10/imthera-medical-inc-receives-fda-approval/ (accessed 03032016)

9 http://www.prnewswire.com/news-releases/apnex-medical-inc-receives-ce-mark-approval-for-hgns-system-to-treat-obstructive-sleep-apnea-132688933.html (accessed 25022016)

10 http://www.bizjournals.com/twincities/blog/in_private/2013/08/venture-backed-med-tech-startup-apnex.html (accessed 23022016)

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers hypoglossal nerve stimulation and in what context and level of care is it provided?

See Element ID B0008

B0008 – What kind of special premises are needed to use hypoglossal nerve stimulation?

Implantation durch HNO Ärzte mit chirurgischer Erfahrung

empfohlen: Universitätskliniken

The implantation of HGNS system should be performed by a specialised otorhinolaryngologist experienced in the surgical technique and postoperative management. The procedure is performed under general anaesthesia in an inpatient setting [21]. Prior to the implementation a drug-induced sleep endoscopy is needed. Prior to and after implantation full-night, in-laboratory diagnostic polysomnographic examinations are required. It is advised that HGNS implantation is restricted to highly specialised centres like University hospitals.

B0009 – What supplies are needed to use hypoglossal nerve stimulation?

OP Raum, Neuromonitoring, Schlaflabor, Endoskopie

For implementation, a sterile operation theatre is needed. The operation itself requires a specialised otorhinolaryngologist with a supporting team as well as a physicist and equipment for neuromonitoring. Several instruments are needed for the intervention (knife for incisions, subcutaneous tunnelling device etc.). It is performed in an inpatient setting. A sleep laboratory and specialists in sleep medicine are required as well as an endoscopy unit. Application of the HGNS device will require a more extensive clinical work-up for diagnostic purposes compared with the current situation.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of hypoglossal nerve stimulation?

derzeit keine Erstattung

Actually, the device implantation for hypoglossal nerve stimulation for the treatment of moderate-to-severe OSA is not included in the Austrian hospital benefit catalogue. Therefore, the intervention itself is not reimbursed by the Austrian health care system.

4 Health Problem and Current Use

Overview of the disease or health condition

A0002 – What is the disease or health condition in the scope of this assessment?

obstruktive Schlafapnoe: schlafbezogene Atmungsstörung durch Kollaps der Rachenmuskulatur

Obstructive sleep apnea (OSA) is caused by repetitive obstruction of the upper airway during sleep, resulting in hypopnea (reduced airflow during sleep) or apnea (complete airflow cessation during sleep) [25]. Airflow obstruction is thought to result from reduction in pharyngeal neuromuscular activity at sleep onset [26, 27]. Because of protective reflexes, the pharyngeal airway maintains patency during wakefulness, but, during sleep, loss of these reflexes reduces the activity of the pharyngeal dilator muscle, causing collapse of the susceptible airway [2]. Collapsibility can also be increased by underlying anatomic alterations. Obesity and particularly central adiposity, both potent risk factors for sleep apnea, can increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues [1].

Apnoe-Hypopnoe-Index: Hinweis auf Schwere der Atmungsstörung

The apnea-hypopnea index (AHI) is commonly used to categorize the severity of OSA and it represents the average number of apneas and/or hypopneas per hour of recorded sleep. In adults, an AHI of 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 [28].

obstruktives Schlafapnoesyndrom (OSAS): AHI ≥5, Tagesschläfrigkeit

An apnea is defined as the complete cessation of airflow for at least 10 seconds. Apneas are further classified as obstructive, central, or mixed, based on whether the effort to breathe is present during the event. A hypopnea is defined as a reduction in airflow that is followed by an arousal from sleep or a decrease in oxyhemoglobin saturation [3]. Commonly used definitions of a hypopnea require a 25% or 50% reduction in oronasal airflow associated either with a reduction in oxyhemoglobin saturation or an arousal from sleep [29].

A0003 – What are the known risk factors for OSA?

Risikofaktoren: Übergewicht, männliches Geschlecht, Alter, erbliche Faktoren

Several risk factors, including obesity, male sex, age, and heritable factors, have been associated with an increased prevalence of obstructive sleep apnea in the general population [30]. Among these, obesity is one of the strongest sleep apnea risk factors [1]. Prevalence of OSA increases with age, particularly in adults older than 60 years [31-34]. The growing rate of obesity also contributes to increasing OSA prevalence [35].

A0004 What is the natural course of OSA?

Tendenz zur Verschlechterung

erhöhtes Sterblichkeitsrisiko

The natural course of the OSA disorder has been investigated only in a few studies [36]. Mild-to-moderate OSA has a tendency to worsen, although patients may improve or remain stable. OSA leads to excessive daytime sleepiness, cognitive dysfunction, impaired work performance, and decrements in health-related quality of life, if left untreated. OSA is associated with adverse clinical outcomes, including cardiovascular disease [3, 37-39], hypertension [40-42], cognitive impairment and metabolic abnormalities, such as type 2 diabetes [3, 43-46]. OSA significantly increases the risk of death from any cause and the increase is independent of other risk factors [39, 47, 48].

Effects of the disease or health condition on the individual and society

A0005 – What are the symptoms and the burden of OSA for the patient?

Symptome: Tagesmüdigkeit, Atemaussetzer, Leistungsabfall, depressive Symptome

Clinical symptoms include unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, insomnia, snoring and cognitive impairment [49, 50]. OSA has been associated with diabetes, an increased cardiovascular and cerebrovascular morbidity and mortality [51].

A0006 – What are the consequences of OSA for the society?

höhere Gesundheitskosten, erhöhtes Unfallrisiko

Patients with OSA have higher rates of health care use, more frequent and longer hospital stays, and greater health care costs than after diagnosis [52, 53]. Excessive daytime sleepiness in OSA has been related to an increased risk of accidents [54-56]. Observational studies indicate that CPAP reduces motor vehicle crash risk among drivers with OSA [57, 58].

Current clinical management of the disease or health condition

A0024 – How is OSA currently diagnosed according to published guidelines and in practice?

Polysomnographie

Polysomnography performed in a sleep laboratory has been the standard method to diagnose OSA [9, 49, 59].

A0025 – How is the OSA condition currently managed according to published guidelines and in practice?

Standardtherapie: kontinuierlicher positiver Atemwegsdruck über Schlafapnoe-Maske

geringe Compliance

The goal of the OSA treatment is to alleviate airway obstruction during sleep. CPAP is currently the universally-accepted standard treatment for moderate-to-severe OSA. The CPAP machine delivers a positive stream of air pressure that acts as a pneumatic splint to maintain the opening of the airway during sleep. The intervention requires patients to wear a nasal or full face mask whilst sleeping. Compliance in the home setting is often poor, with only 40 to 60 per cent of patients using the treatment long-term or as prescribed. When adherence is defined as greater than 4 hours of nightly use, 46 to 83% of patients with obstructive sleep apnea have been reported to be nonadherent to treatment [60-62].

Other treatment options (oral appliance therapy, positional therapy, weight loss, and upper airway reconstructive surgery) are available for selected patients, but the treatment effect is frequently incomplete [63]. Upper airway surgery, a treatment option for carefully selected patients with OSA, aims at reducing anatomical upper airway obstruction in the nose, oropharynx and hypopharynx [22]. But long-term follow-up studies have suggested that the initial effect of surgery may lessen over time [23].

Target population

A0007 – What is the target population in this assessment?

The target population are patients with moderate-to-severe OSA who do not tolerate CPAP and do not adhere to therapy for many reasons like discomfort, skin irritation, noise and claustrophobia [25, 64-66].

Zielgruppe: Zweitlinientherapie nach CPAP für mittel-bis schwergradiges OSAS

A0023 – How many people belong to the target population?

Large population-based prevalence studies of predominately white populations estimate the prevalence of the OSA syndrome at approximately 3–4% in men and 2% in women [30, 32, 33, 67]. The OSA syndrome is characterised by both an AHI ≥5 along with daytime sleepiness [28]. In the Wisconsin Sleep Cohort Study, the prevalence of OSA, based on an AHI of >15 in people aged 30 to 60 years, was 9.1% in men and 4.0% in women [30]. However, specific data for Austria are not available.

Prävalenz OSAS 3-4 % bei Männern, 2 % bei Frauen

There is no information available on how many patients with moderate-to-severe OSA, not tolerating or not adhering to CPAP therapy, are potential candidates for HGNS therapy belonging to the subgroup of currently untreated patients.

A0011 – How much are the technologies utilised?

According to the description of the application form we received from the Austrian Ministry of Health ("Verwaltung von Änderungs- und Ergänzungsvorschlägen zum Leistungskatalog des BMG", VAEV), the anticipated volume of implanted devices is estimated at 15 per year while 3 procedures were performed in the past year. The given information applies only to the applicants' hospital, data of expected frequencies for Austria are lacking.

erwartet: 15 Eingriffe/Jahr (1 Krankenanstalt)

5 Clinical effectiveness

5.1 Outcomes

wesentliche Endpunkte für Wirksamkeit:

The following outcomes were defined as crucial to derive a recommendation:

- Severity of obstructive sleep apnea (AHI)
- Level of daytime sleepiness (e.g. Epworth Sleepiness Scale)
- Quality of life

Schwere der OSA (AHI Index)

Tagesschläfrigkeit

Lebensqualität

Cardiovascular morbidity and mortality are relevant clinical endpoints that were not taken into consideration given the early phase of development of HGNS.

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 [28]. 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 no studies addressing health outcomes like cardiovascular morbidity or 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 [68].

Epworth Sleepiness Scale: validiertes Messinstrument für Tagesschläfrigkeit

The Epworth Sleepiness Scale [69] 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 [70, 71]. 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 [59]. 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.

5.2 Included studies

Study and patient characteristics

2 RCTs identifiziert:

1 RCT zu HNS/HGNS® abgebrochen nach ungünstiger Interimanalyse

1 RCT zu Inspire® mit withdrawal design in Therapierespondern

For evaluating efficacy-related outcomes we called for RCTs. We identified two RCTs, one with a therapy withdrawal design [14] of a consecutive cohort of treatment responders (randomised subset) from a prospective single arm study of 126 implanted participants [16]. After completion of the 12-month follow-up, the first 46 therapy responders entered the withdrawal study. Participants were randomised to either therapy maintenance ("ON") group or therapy withdrawal ("OFF") group for a minimum of 1 week. Another RCT [15], a multicentre study, was prematurely closed by the company following an unfavourable interim analysis after 6 months. Participants were randomly allocated on a 2:1 basis to have the device activated 1 month or 7 months postimplantation. The 6 month results from 21 patients from an Australian centre were reported in an abstract only. Although unconventional, we included the abstract to avert selective reporting and due to limited information, we refrained from assessing the risk of bias.

insgesamt 67 PatientInnen, Alter 53–57 Jahre, mehrheitlich Männer

Both studies with a total of 67 participants reported outcomes at 6 months, the withdrawal study reported also outcomes after 1 week of therapy maintenance and therapy withdrawal. The mean age of patients ranged from 53 and 57 years. The minority of patients were females (11-19%), the loss to follow-up rate was 0%. The inclusion criteria differed between the two studies; the withdrawal study included only therapy responders with at least 50% reduction of AHI from baseline and AHI less than 20 events per hour. Originally, patients included in the single arm study [16] had to have an AHI >20 to 50 events per hour without a complete concentric collapse at the retropalatal airway observed in DISE, whereas the second RCT included participants with an AHI of 20 to 80 events per hour.

Inspire® UAS System was implanted in the withdrawal study [14], HNS/HGNS® System in the other trial [15].

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table 7-1. Due to insufficient information, we could not assess the risk of bias of the RCT reported only in an abstract [15].

5.3 Results

Mortality

D0001 – What is the expected beneficial effect of hypoglossal nerve stimulation on mortality?

keine Evidenz zu Endpunkt Mortalität

Cardiovascular and all-cause mortality is a relevant outcome for assessing the clinical effectiveness of hypoglossal nerve stimulation in treating moderate-to-severe OSA. Due to the lack of long-term studies, the effectiveness on mortality is unknown. No evidence was found to answer the research question.

Morbidity

D0005 – How does hypoglossal nerve stimulation affect symptoms and findings (severity, frequency) of moderate-to-severe OSA?

Endpunkte AHI, ESS:

Answering this research question was based on the outcomes "AHI" and "ESS". The difference in AHI and ESS was reported in both RCTs [14, 15]. After 1 week, the AHI in the "on-treatment" group was statistically significant, lower [-16.9 (95% CI -24.7, -9.0)] than in the "off treatment" group [14]. Both groups consisted only of treatment responders. After 6 months, the treatment was resumed in both groups, the AHI showed no statistically significant difference between groups [14]. In contrast, after 6 months, the AHI showed no statistically significant difference between the "device active" and the control group in previously "treatment naïve" participants [15].

Anstieg eine Woche nach Therapieentzug in Therapierespondern

ohne Präselektion nach Therapieansprechen kein Unterschied mit/ohne Stimulation nach 6 Monaten

Data regarding AHI are valid only for a short period of 6 months but not in the long-term.

After 1 week, the ESS in the "on-treatment" group was lower [-4.5 (95% CI -7.5, -1.4)] than in the "off treatment" group, which was statistically significant [60]. After 6 months, the treatment was resumed in both groups and the ESS showed no statistically significant difference between groups [60]. In contrast, after 6 months, the ESS showed no statistically significant difference between the "device active" and the control group in previously "treatment naïve" participants [62].

D0006 – How does hypoglossal nerve stimulation affect progression (or recurrence) of moderate-to-severe OSA?

Answering this research question was based on the "AHI" outcome in both RCTs. See Element ID D0005.

Function

D0011 – What is the effect of hypoglossal nerve stimulation on patients' body functions?

keine Evidenz hinsichtlich Endpunkte zur Funktion

Moderate-to-severe OSA affects the cardiovascular system and is associated with diabetes and cognitive impairment. Thus, answering this research question is relevant but has been defined as not feasible. No evidence was found to answer the research question. The effect of hypoglossal nerve stimulation on functioning has not been studied.

D0016 – How does the use of hypoglossal nerve stimulation affect activities of daily living?

The treatment with HGNS affects daytime sleepiness in daily life activities and functional outcomes relevant to daily behaviours in moderate-to-severe OSA. See Element ID D0005 and Element ID D0013.

Health-related quality of life

D0012 – What is the effect of hypoglossal nerve stimulation on generic health-related quality of life?

keine Evidenz zu generischer QoL

No evidence was found to answer this research question (no identified study reported generic health-related quality of life).

D0013 – What is the effect of hypoglossal nerve stimulation on disease-specific quality of life?

Reduktion der krankheitsspezifischen QoL eine Woche nach Therapieentzug in Therapierespondern

The disease specific quality of life was reported in one RCT [14]. After 1 week, the FOSQ in the "on treatment" group was increased in a statistically significant way by 2.9 (95% CI 0.8, 5.0) compared to the "off-treatment" group (2.0 points increase is considered a minimally important difference). After 6 months, the treatment was resumed in both groups, the FOSQ showed no statistically significant difference between groups.

Patient satisfaction

D0017 – Were patients satisfied with the hypoglossal nerve stimulation?

To answer this research question, the outcome "FOSQ" was used. The effect of HGNS on disease specific quality of life has already been addressed in the previous section. See Element ID D0013.

6 Safety

6.1 Outcomes

wesentliche Endpunkte für Sicherheit:

(Schwere) unerwünschte Effekte (S)AE

Schwere produktbezogene unerwünschte Effekte – (SADE)

The following outcomes were defined as crucial to derive a recommendation:

- Adverse events (AE)
- Serious Adverse Events (SAE)
- Serious adverse device effects (SADE)

In accordance with the guidelines of medical devices on serious adverse event reporting, these outcomes have been selected.[11]

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 medic al 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.

6.2 Included Studies

Study and patient characteristics

7 prospektive Einzelarmstudien mit insgesamt 224 PatientInnen

For evaluating safety-related outcomes, we accepted RCTs, prospective case-series with more than 10 patients and length of follow-up of more than 6 months, and registries with more than 100 patients.

However, we could not identify any controlled trials reporting safety outcomes of hypoglossal nerve stimulation for the treatment of moderate-to-severe OSA. The only studies that met our inclusion criteria are seven single-arm studies with a total of 224 patients assessing the safety of hypoglossal nerve stimulation [16-21, 72].

[11] http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf

Alter im Durchschnitt 50–55 Jahre, mehrheitlich Männer, Follow-Up bis 3 Jahre

The mean age of patients differed between 50 and 55 years [21] [16]. The minority of patients was females (3-35%) [20, 72]. The follow-up of studies was 6 months [19, 72], 12 months up to 20 months [16, 17, 20, 21] and 36 months (3 years) [18]. The loss to follow-up rate differed between 2 and 11% [16, 72].

One trial reported safety outcomes at 12 months [16], at 18 months [17], and 36 months [18] for 126 patients. One trial reported safety outcomes at 6 months for 21 patients [19] and at 12 months for 32 patients (including 21 patients from [19]) [20].

2 Studien (4 Publikationen) zu Inspire®

eine Studie (2 Publikationen) zu HNS/HGNS® eine Studie zu Aura6000™

Inspire® UAS Systems (Inspire Medical, Inc.) were implanted in two trials with 4 publications [16-18, 72], HNS/HGNS® Systems (Apnex Medical, Inc.) were implanted in one trial with 2 publications [19, 20] and Aura6000TM Systems (ImThera Medical, Inc.) were implanted in one trial [21].

Population in allen Studien: mittel- bis schwergradige OSA nach erfolgloser CPAP Therapie

All studies included patients with moderate-to-severe OSA with failure or intolerance of CPAP treatment. One trial included patients with an AHI between 20 and 100 per hour, with ≥15/h occurring in NREM sleep and a predominance of hypopneas (≥80%) as a proportion of the sum of apnea and hypopnea events [19, 20]. One study included patients with AHI ≥25/h in the first part, in the second part only selected patients based on predictors of therapy response in Part 1 were included (AHI between 20-50/h, without complete concentric collapse at the level of soft palate, determined by drug-induced sleep endoscopy) [72]. One study included patients with AHI ≥20/h and no preferential selection of subjects for apnoea or hypopnoea indices [21], but excluded patients with clinically enlarged tonsils (grade 3 or 4) and the presence of obstructive nasal polyps. One trial included patients with an AHI greater than 20 to 50/h without complete concentric collapse at the retropalatal airway observed in DISE [16-18].

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table 7-1.

6.3 Results

Patient safety

C0008 – How safe is hypoglossal nerve stimulation in comparison to the comparator(s)?

No studies were identified that are directly comparing hypoglossal nerve stimulation for the treatment of OSA with no intervention.

Bandbreite der Komplikationsraten:

SADE 2–23 %
Explantationen 2–13 %

In the single-arm studies, serious adverse device effects (SADE) occurred in 7-10% of patients, the device was explanted in 6-7% of patients at 6 months [19, 72]. At 12-20 months, SADE occurred in 2-23% of patients, the device was explanted in 1-13% of patients [16, 20, 21]. At 40 months, SADE occurred in 2% of patients, the device was explanted in 2% of patients [18]. Serious adverse device effects included adverse events like infection, device explantation, cuff dislodgement, spinal accessory nerve damage, broken leads, defective pulse generator and device revision, but no deaths occurred.

Overall adverse events (procedure or device/therapy-related) are not reported in percentage of patients, but only in terms of events per study population. Because of unclear reporting, data may be imprecise.

At 6 months, 15 events occurred in 31 patients, respectively 66 events in 21 patients [19, 72]. At 12 to 18 months, 64 events occurred in 14 patients, respectively 392 events in 126 patients [17, 21]. 469 events occurred in 126 patients at 40 months [18]. Very frequently occurring upcoming events were discomfort due to electrical stimulation, tongue abrasion, tongue soreness, temporary tongue weakness and post-operative discomfort related to incisions.

unerwünschte Ereignisse häufig bis zu 469 Ereignisse in 126 PatientInnen nach 40 Monaten

Serious adverse events (SAE) (procedure or device/therapy-related) occurred in 10-14% of patients at 6 months [19, 72], at follow-up 12-18 months, rates ranged from 21 to 29% [17, 21].

SAE 10–14 % nach 6 Monaten; 21–29 % nach 12-18 Monaten

C0004 – How does the frequency or severity of harms change over time or in different settings?

No direct evidence was found to answer this research question in an appropriate way.

However, it seems likely that the frequency and/or severity of harms decrease over time. The identified study with the longest duration and the most patients reported 343 adverse events in the first year, 49 in the following 6 months and 77 in the following 22 months [18].

Mehrheit der unerwünschten Ereignisse im ersten Jahr

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of hypoglossal nerve stimulation?

No direct evidence was found to answer this research question.

C0007 – Is hypoglossal nerve stimulation associated with user-dependent harms?

No direct evidence was found to answer this research question. However, in all included studies, hypoglossal nerve stimulation was implanted by experienced specialised otolaryngologists.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of hypoglossal nerve stimulation?

No literature was retrieved that identified specific data or monitoring records of outcomes for the treatment of OSA.

7 Quality of evidence

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [24] for each endpoint individually. Each study was rated by two independent researchers (ISF, AK). In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [24].

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.

The ranking according to the GRADE scheme for the research question can be found in Table 7-1.

Overall the strength of evidence for the effectiveness and safety of hypoglossal nerve stimulation is low to very low.

Table 7-1: Evidence profile: efficacy and safety of hypoglossal nerve stimulation in patients with moderate-to-severe obstructive sleep apnea

No of studies/ patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy: HNS stimulation vs no stimulation							
Apnea-hypopnea index (AHI) (difference between groups)							
2/67	RCT 1: withdrawal design, only responders included, control group device off for 1 week RCT 2: device implanted, control group device not activated	Difference between groups: after 1 week: -16.9 (s.s.) at 6 months: -7.6 (n.s.)	Serious limitations (-1)[12]	No important inconsistency	Some uncertainty (-1)[13]	Imprecise data (-1)[14]	Very low
Oxygen Desaturation Index (ODI) (difference between groups)							
2/67	RCT 1: withdrawal design, only responders included, control group device off for 1 week RCT 2: device implanted, control group device not activated	Difference between groups: after 1 week: -15.1 (s.s.) at 6 months: n.s.	Serious limitations (-1)[12]	No important inconsistency	Some uncertainty (-1)[13]	Imprecise data (-1)[14]	Very low
Functional Outcomes of Sleep Questionnaire (FOSQ) (difference between groups)							
1/46	RCT 1: withdrawal design, only responders included, control group device off for 1 week	Difference between groups: after 1 week: 2.9 (s.s.)	Serious limitations (-1)[12]	n/a (only 1 trial)	Some uncertainty (-1)[13]	Imprecise data (-1)[14]	Low
Epworth Sleepiness Scale (ESS) (difference between groups)							
2/67	RCT 1: withdrawal design, only responders included, control group device off for 1 week RCT 2: device implanted, control group device not activated	Difference between groups: after 1 week: -4.5 (s.s.) at 6 months: n.s.	Serious limitations (-1)[12]	No important inconsistency	Some uncertainty (-1)[13]	Imprecise data (-1)[14]	Very low

[12] Randomisation and allocation concealment unclear

[13] RCT 1 included only responders to the treatment

[14] Small sample size

No of studies/ patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Safety							
Serious Adverse Device Effects (in% of pts)							
2/52	Single-arm studies	at 6 mo: 7-10% System explants 6-7%	No serious limitations	No important inconsistency	Direct	None	Low
3/172	Single-arm studies	12-20 mo: 2-23% System explants 1-13%	No serious limitations	Important inconsistency(-1)[15]	Direct	None	Very low
1/126	Single-arm study	at 40 mo: 2% System explants 2%	No serious limitations	n/a (only 1 trial)	Direct	None	Low
Adverse Events (events/study population)							
2/52	Single-arm studies	at 6 mo:15/31; 66/21	No serious limitations	No important inconsistency	Direct	Imprecise data (-1)[16]	Very low
2/140	Single-arm studies	12-18 mo: 64/14; 392/126	No serious limitations	No important inconsistency	Direct	Imprecise data (-1)[16]	Very low
1/126	Single-arm study	at 40 mo: 469/126	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[16]	Very low
Serious Adverse Events (in % of pts)							
2/52	Single-arm studies	at 6 mo:10-14%	No serious limitations	No important inconsistency	Direct	Imprecise data (-1)[16]	Very low
2/140	Single-arm studies	12-18 mo: 21-29%	No serious limitations	No important inconsistency	Direct	Imprecise data (-1)[16]	Very low

s.s. = statistically significant; n.s. = not significant; mo = months; pts = patients

[15] The difference between the lowest and the highest percentage of system explants was more than 20%

[16] Double counting of events possible because of unclear reporting

8 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 airway dilator muscles. Obesity and particularly central adiposity, both potent risk factors for sleep apnea, can also increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues. OSA is associated with adverse clinical outcomes, including cardiovascular disease, hypertension, cognitive dysfunction and metabolic abnormalities, such as type 2 diabetes as well as with an increased risk of traffic accidents. CPAP is currently the universally-accepted standard treatment for moderate-to-severe OSA, but long-term compliance is limited and estimated to be in the order of 50%. Novel treatments, like hypoglossal nerve stimulation, inducing substantial reduction of OSA may provide a possibility to treat a part of this subgroup of currently untreated patients.

obstruktive Schlafapnoe: schlafbezogene Atmungsstörung durch Kollaps der Rachenmuskulatur

CPAP ist Standardtherapie aber Langzeitcompliance nur bei etwa 50 %

The aim of this report was to assess the clinical effectiveness and safety of hypoglossal nerve stimulation in patients with moderate-to-severe obstructive sleep apnoea refractory to CPAP. Two RCTs were available to assess the clinical efficacy of hypoglossal nerve stimulation in comparison to no intervention. Seven case series were available to assess safety, since RCTs did not report any safety outcomes.

2 RCT zur Wirksamkeit, 7 Fallserien zur Sicherheit der Stimulation des Nervus hypoglossus

Both RCTs included 67 patients with moderate-to-severe OSA but their inclusion criteria differed from each other [14, 15]. Responders in both trials were defined as achieving an AHI <20 with at least 50% reduction from baseline.

One RCT had a withdrawal design [14]. After completion of 12-month follow up in an uncontrolled prospective study [16], 46 consecutive patients, classified as 'responders', were selected and were randomly allocated to either one week therapy-withdrawal subgroup or therapy-maintenance subgroup. The a priori defined criteria for the single arm study excluded patients with a complete concentric collapse at the retropalatal airway observed in drug-induced sleep endoscopy and therefore, this exclusion criterion applies also to the randomised subgroup.

1 RCT mit Therapieentzugs-Design in 46 HNS-Therapierespondern

It is unclear whether the second trial applied such exclusion criterion [15] because the only available information was from the registry, the database of clinical research studies [17] and a published abstract with study results of 21 patients. The study has been terminated by the company following an unfavourable interim analysis after 6 months. The intervention group was implanted with the HNS/HGNS® System (Apnex Medical, Inc.) and simulation was turned on at 1 month post-implant. In the control group, likewise implanted with the system, therapy would have turned on at 7 months post-implant. After six months, the efficacy-related outcomes failed to show a between-group difference in the reduction of OSA severity, owing to major unanticipated improvements in the control group. Both groups showed a considerable reduction in AHI, but the underlying cause of improvement of AHI in the control group remains unknown.

1 RCT vorzeitig beendet 21 PatientInnen implantiert – Randomiserung auf Einschalten nach 1 bzw. 7 Monaten

beide Gruppen zeigen Verbesserung der Symptome (AHI) nach 6 Monaten

[17] https://clinicaltrials.gov/ct2/show/record/NCT01446601

1 wöchiger Therapieentzug in Therapierespondern führt zur Verschlechterung der Symptome (AHI, ESS)

The therapy-withdrawal RCT subgroup [14] discontinued the treatment for 1 week. After 1 week, patients resumed the treatment for a six months follow-up period, respectively an overall 18 months follow-up period. The withdrawal of the stimulation therapy within 1 week resulted in worsening of all efficacy-related outcomes. When therapy was resumed, outcomes showed no difference between either of the groups at 18 months.

Both RCTs are flawed by small sample sizes and the inherent lack of blinding of hypoglossal nerve stimulation therapy. There is a high risk of bias in the withdrawal RCT associated with highly selected participants, not representative of the population affected by OSA. Participants were recruited from an industry-sponsored, uncontrolled study and selected patients classified as 'responders' only for the trial population were included. Furthermore, a one week off therapy period does not allow long-term efficacy to be assessed [14].

Therapieentzugdesign erlaubt keine Bewertung der Wirksamkeit in Zielpopulation

In highly selected responders, the effects of withdrawal and resuming the therapy were attributable to hypoglossal nerve stimulation. However, the study design and the selection of responders do not allow assessing the relative effectiveness of the intervention. As responders do not represent the target population in this report, the study results cannot be used as evidence to derive a recommendation.

Charakteristika der Therapieresponder unklar

Furthermore, it is known that a subset of patients will respond to stimulation therapy anyway, but who the responders are, how many of them will respond and how effective hypoglossal nerve stimulation is remain unknown. And, important information about the non-responders is lacking.

2. RCT zeigt Verbesserung auch in Kontrollgruppe

The effect of stimulation therapy shown in responders was not reproducible in another study population eligible for the stimulation therapy. The underlying cause of improvement of severity of OSA independent of active stimulation remains unclear.

Seven publications of four case series met our inclusion criteria to assess safety-related outcomes [16-21].

unerwünschte Ereignisse häufig

bis zu 469 Ereignisse in 126 PatientInnen nach 40 Monaten

The most prominent adverse events (AE) included tongue abrasions, tongue soreness or weakness and stimulation related discomfort. The most recent and largest study reported 469 adverse events in 126 participants at 40 months. Both the rate of device-related and the rate of procedure-related adverse effects are reported to decrease over time after implantation. More than half of the patients complained about discomfort due to electrical stimulation and one third about tongue abrasion, which required further adjustment of simulation parameters and dental adjustments [18].

schwere produktbezogene Ereignisse: Wundinfektionen, Elektrodenbrüche; E.-dislokationen; defekte Generatoren, Geräterevisionen

Serious adverse device effects (SADE) included wound infections, electrode fracture, lead and cuff dislodgement, defective pulse generator and device revision. The percentage of device explantations showed a high variability, ranging from 2% in the largest study [18] to 13% in a small study with 32 participants [20], and it appears to depend on the appropriate technique applied, in particular, on the placement of stimulation electrodes. Device related deaths did not occur; three deaths, but classified as unrelated to the implantation, were reported at 40 months follow-up [18].

Although the strength of evidence for safety is very low, hypoglossal nerve stimulation for treatment of OSA does not seem to be related with lethal consequences. However, it causes a high number of non-serious adverse events and less frequent serious adverse events.

The influence of technical properties of different hypoglossal nerve stimulation systems on the reported outcomes cannot be assessed, but appears to play a minor role. Appropriate patient selection appears to be essential for the success of therapy, but exact criteria for optimal patient selection are lacking because patient characteristics of responders are known incompletely. The available data may suggest that incorrect patient selection provides a major limitation.

Therapieerfolg abhängig von optimaler Patientenselektion, jedoch keine Informationen zu Kriterien

Additional parameters that might predict response and could then improve patient selection need to be determined. Data also suggest that hypoglossal nerve stimulation usually produces only a partial response and does not offer a cure for the patient from the disease.

Stimulation führt zu keiner Heilung, dauerhafte Behandlung notwendig

Finally, the strength of evidence for efficacy and safety is low to very low regarding patient benefits and harms. Severe device-related adverse effects appear to be relatively rare. Information on device durability beyond 40 months is lacking. Furthermore, long-term data regarding treatment effects, complications and compliance are lacking, and none of the relevant clinical endpoints like cardiovascular morbidity or mortality were reported.

schwere produktbezogene Komplikationen selten

Currently, there is one registered ongoing randomised controlled trial (NCT02263859) with an open-label design for a four-month period. [18] Both groups will be implanted with the Aura6000™ System (ImThera Medical, Inc.). The estimated enrolment comprises 141 participants with a 12 month follow-up period. The primary completion is planned in May 2016, longer term data may become available as final completion is listed for May 2021.

2 registrierte/geplante RCTs mit Studienende 2016

Another randomised controlled trial with delayed therapy activation with a 6-month follow-up is mentioned in the dossier of the manufacturer provided for evaluation at LBI-HTA. Ongoing enrolment of 40 patients will be completed by 2016. Both groups will be implanted with the Inspire® UAS System (Inspire Medical, Inc.). The trial is not listed in the 3 databases with registered clinical trials. [19]

One major weakness of the systematic review is the incompleteness of available information on the study which has been terminated by the company following an unfavorable interim analysis. Nevertheless, we decided to include the RCT to avert selective reporting. But, due to limited information provided by the abstract only, we were not able to assess the risk of bias. The impact on the assessment is unclear, but the chance of modification is considered to be low.

Limitation des Reviews: wenig Informationen über abgebrochenen RCT, da nur Konferenzabstracts verfügbar

[18] https://clinicaltrials.gov/ct2/show/NCT02263859

[19] ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials (EUdraCT)

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: 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:

The current evidence is not sufficient to prove that hypoglossal nerve stimulation for treating moderate-to-severe obstructive sleep apnea is more effective and equally safe than no treatment. New study results will potentially influence the effect estimate considerably.

Evidenz derzeit nicht ausreichend für Empfehlung

The re-evaluation is recommended in 2018.

Re-evaluation 2018

10 References

[1] Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. Proceedings of the American Thoracic Society. 2008;5(2):185-92.

[2] Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet (London, England). 2014;383(9918):736-47.

[3] Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proceedings of the American Thoracic Society. 2008;5(2):136-43.

[4] Rosario IC. Obstructive sleep apnea: a review and update. Minnesota medicine. 2011;94(11):44-8.

[5] White DP. Pathogenesis of obstructive and central sleep apnea. American journal of respiratory and critical care medicine. 2005;172(11):1363-70.

[6] Eisele DW, Smith PL, Alam DS, Schwartz AR. Direct hypoglossal nerve stimulation in obstructive sleep apnea. Archives of otolaryngology – head & neck surgery. 1997;123(1):57-61.

[7] Goding GS, Jr., Eisele DW, Testerman R, Smith PL, Roertgen K, Schwartz AR. Relief of upper airway obstruction with hypoglossal nerve stimulation in the canine. Laryngoscope. 1998;108(2):162-9.

[8] Schwartz AR, Bennett ML, Smith PL, De Backer W, Hedner J, Boudewyns A, et al. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. Archives of otolaryngology – head & neck surgery. 2001;127(10):1216-23.

[9] S3-Leitlinie. Nicht erholsamer Schlaf – Schlafstörungen. AWMF-Register Nr. 063/001. Stand: 01.10.2009 (in Überarbeitung), gültig bis 01.12.2012 [cited 26.2.2016]. Available from: http://www.awmf.org/uploads/tx_szleitlinien/063-001l-abgelaufen.pdf.

[10] American Academy of Sleep Medicine. Obstructive Sleep Apnea. [cited 21.2.2016]. Available from: http://www.aasmnet.org/resources/factsheets/sleepapnea.pdf.

[11] Steier J, Seymour J, Rafferty GF, Jolley CJ, Solomon E, Luo Y, et al. Continuous transcutaneous submental electrical stimulation in obstructive sleep apnea: A feasibility study. Chest. 2011;140(4):998-1007.

[12] Randerath WJ, Galetke W, Domanski U, Weitkunat R, Ruhle KH. Tongue-muscle training by intraoral electrical neurostimulation in patients with obstructive sleep apnea. Sleep. 2004;27(2):254-9.

[13] Smith PL, Eisele DW, Podszus T, Penzel T, Grote L, Peter JH, et al. Electrical stimulation of upper airway musculature. Sleep. 1996;19(10 SUPPL.):S284-S7.

[14] Woodson BT, Gillespie MB, Lin HS, Baskin JZ, Padhya TA, Soose RJ, et al. Randomized treatment withdrawal of hypoglossal nerve stimulation for obstructive sleep apnea. Otolaryngology – Head and Neck Surgery (United States). 2014;151(1):P134-P5.

[15] Smart K, O'Donoghue F, Worsnop C, Collins A, Barnes M. Short term outcomes for obstructive sleep apnoea patients treated with hypoglossal nerve stimulation. Sleep and Biological Rhythms. 2013;11 ((Smart K.; O'donoghue F.; Worsnop C.; Collins A.; Barnes M.) Institute of Breathing and Sleep, Melbourne, Australia):68-9.

[16] Strollo PJ, Jr., Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, et al. Upper-airway stimulation for obstructive sleep apnea. New England Journal of Medicine. 2014;370(2):139-49.

[17] Strollo PJ, Gillespie MB, Soose RJ, Maurer JT, de Vries N, Cornelius J, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18 Months. Sleep. 2015;38(10):1593-8.

[18] Woodson BT, Soose RJ, Gillespie MB, Strohl KP, Maurer JTM, de Vries N, et al. Three-Year Outcomes of Cranial Nerve Stimulation for Obstructive Sleep Apnea: The STAR Trial. Otolaryngology – head and neck surgery: official journal of American Academy of Otolaryngology – Head and Neck Surgery. 2016;154(1):181-8.

[19] Eastwood PR, Barnes M, Walsh JH, Maddison KJ, Hee G, Schwartz AR, et al. Treating obstructive sleep apnea with hypoglossal nerve stimulation. Sleep. 2011;34(11):1479-86.

[20] Kezirian EJ, Goding GS, Jr., Malhotra A, O'Donoghue FJ, Zammit G, Wheatley JR, et al. Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes. J Sleep Res. 2014;23(1):77-83.

[21] Mwenge GB, Rombaux P, Dury M, Lengele B, Rodenstein D. Targeted hypoglossal neurostimulation for obstructive sleep apnoea: A 1-year pilot study. European Respiratory Journal. 2013;41(2):360-7.

[22] EUnetHTA Joint Action 2 WP. Levels of evidence: Internal validity (of randomized controlled trials). 2013 [cited 20.1.2016]. Available from: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[23] Guo B, Moga C, Harstall C, Schopflocher D. A principal component analysis is conducted for a case series quality appraisal checklist. Journal of clinical epidemiology. 2016;69:199-207.e2.

[24] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

[25] Qaseem A, Holty JE, Owens DK, Dallas P, Starkey M, Shekelle P. Management of obstructive sleep apnea in adults: A clinical practice guideline from the American College of Physicians. Annals of internal medicine. 2013;159(7):471-83.

[26] Fogel RB, Trinder J, White DP, Malhotra A, Raneri J, Schory K, et al. The effect of sleep onset on upper airway muscle activity in patients with sleep apnoea versus controls. The Journal of physiology. 2005;564(Pt 2):549-62.

[27] Schwartz AR, Barnes M, Hillman D, Malhotra A, Kezirian E, Smith PL, et al. Acute upper airway responses to hypoglossal nerve stimulation during sleep in obstructive sleep apnea. American journal of respiratory and critical care medicine. 2012;185(4):420-6.

[28] Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of Obstructive Sleep Apnea: a Population-based Perspective. Expert review of respiratory medicine. 2008;2(3):349-64.

[29] Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22(5):667-89.

[30] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. The New England journal of medicine. 1993;328(17):1230-5.

[31] Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. Sleep. 1991;14(6):486-95.

[32] Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. American journal of respiratory and critical care medicine. 1998;157(1):144-8.

[33] Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, et al. Prevalence of sleep-disordered breathing in women: effects of gender. American journal of respiratory and critical care medicine. 2001;163(3 Pt 1):608-13.

[34] Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Archives of internal medicine. 2002;162(8):893-900.

[35] Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. Journal of applied physiology (Bethesda, Md: 1985). 2005;99(4):1592-9.

[36] Pendlebury ST, Pepin JL, Veale D, Levy P. Natural evolution of moderate sleep apnoea syndrome: significant progression over a mean of 17 months. Thorax. 1997;52(10):872-8.

[37] Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet (London, England). 2005;365(9464):1046-53.

[38] Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. American journal of respiratory and critical care medicine. 2001;163(1):19-25.

[39] Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. The New England journal of medicine. 2005;353(19):2034-41.

[40] Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. Jama. 2000;283(14):1829-36.

[41] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. The New England journal of medicine. 2000;342(19):1378-84.

[42] Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Archives of internal medicine. 1997;157(15):1746-52.

[43] Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. Archives of internal medicine. 2005;165(4):447-52.

[44] Caples SM, Gami AS, Somers VK. Obstructive sleep apnea. Annals of internal medicine. 2005;142(3):187-97.

[45] Gruber A, Horwood F, Sithole J, Ali NJ, Idris I. Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. Cardiovascular diabetology. 2006;5:22.

[46] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. American journal of respiratory and critical care medicine. 2002;165(9):1217-39.

[47] Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS medicine. 2009;6(8):e1000132.

[48] Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep. 2008;31(8):1071-8.

[49] Qaseem A, Dallas P, Owens DK, Starkey M, Holty JE, Shekelle P. Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. Annals of internal medicine. 2014;161(3):210-20.

[50] Mitler MM. Daytime sleepiness and cognitive functioning in sleep apnea. Sleep. 1993;16(8 Suppl):S68-70.

[51] Gami AS, Somers VK. Obstructive sleep apnoea, metabolic syndrome, and cardiovascular outcomes. European heart journal. 2004;25(9):709-11.

[52] Gupta RM, Parvizi J, Hanssen AD, Gay PC. Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: a case-control study. Mayo Clinic proceedings. 2001;76(9):897-905.

[53] Practice parameters for the indications for polysomnography and related procedures. Polysomnography Task Force, American Sleep Disorders Association Standards of Practice Committee. Sleep. 1997;20(6):406-22.

[54] Howard ME, Desai AV, Grunstein RR, Hukins C, Armstrong JG, Joffe D, et al. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. American journal of respiratory and critical care medicine. 2004;170(9):1014-21.

[55] Karimi M, Eder DN, Eskandari D, Zou D, Hedner JA, Grote L. Impaired vigilance and increased accident rate in public transport operators is associated with sleep disorders. Accident; analysis and prevention. 2013;51:208-14.

[56] Tregear S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2009;5(6):573-81.

[57] Tregear S, Reston J, Schoelles K, Phillips B. Continuous positive airway pressure reduces risk of motor vehicle crash among drivers with obstructive sleep apnea: systematic review and meta-analysis. Sleep. 2010;33(10):1373-80.

[58] Karimi M, Hedner J, Habel H, Nerman O, Grote L. Sleep apnea-related risk of motor vehicle accidents is reduced by continuous positive airway pressure: Swedish Traffic Accident Registry data. Sleep. 2015;38(3):341-9.

[59] Huppmann M, Schreiber W, Moder G, Fugger B, Kapfhammer G, Stiebellehner L. [Recommendations for ambulatory polygraphy by the Austrian Pneumology Society]. Wiener klinische Wochenschrift. 2007;119(9-10):326-30.

[60] Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proceedings of the American Thoracic Society. 2008;5(2):173-8.

[61] McArdle N, Devereux G, Heidarnejad H, Engleman HM, Mackay TW, Douglas NJ. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. American journal of respiratory and critical care medicine. 1999;159(4 Pt 1):1108-14.

[62] Gay P, Weaver T, Loube D, Iber C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep. 2006;29(3):381-401.

[63] Dedhia RC, Strollo PJ, Soose RJ. Upper Airway Stimulation for Obstructive Sleep Apnea: Past, Present, and Future. Sleep. 2015;38(6):899-906.

[64] Chasens ER, Pack AI, Maislin G, Dinges DF, Weaver TE. Claustrophobia and adherence to CPAP treatment. Western journal of nursing research. 2005;27(3):307-21.

[65] Parthasarathy S, Haynes PL, Budhiraja R, Habib MP, Quan SF. A national survey of the effect of sleep medicine specialists and American Academy of Sleep Medicine Accreditation on management of obstructive sleep apnea. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2006;2(2):133-42.

[66] Veasey SC, Guilleminault C, Strohl KP, Sanders MH, Ballard RD, Magalang UJ. Medical therapy for obstructive sleep apnea: a review by the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep. 2006;29(8):1036-44.

[67] Bearpark H, Elliott L, Grunstein R, Cullen S, Schneider H, Althaus W, et al. Snoring and sleep apnea. A population study in Australian men. American journal of respiratory and critical care medicine. 1995;151(5):1459-65.

[68] Diagnosis and Treatment of Obstructive Sleep Apnea in Adults. AHRQ Publication No. 11-EHC052 July 2011 [cited 9.12.2015]. Available from: https://www.effectivehealthcare.ahrq.gov/ehc/products/117/683/CER32_SleepApnea_FinalReview_201108.pdf.

[69] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.

[70] Johns M, Hocking B. Daytime sleepiness and sleep habits of Australian workers. Sleep. 1997;20(10):844-9.

[71] Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res. 2000;9(1):5-11.

[72] Van de Heyning PH, Badr MS, Baskin JZ, Cramer Bornemann MA, De Backer WA, Dotan Y, et al. Implanted upper airway stimulation device for obstructive sleep apnea. Laryngoscope. 2012;122(7):1626-33.

[73] Gartlehner G. Internes Manual. Abläufe und Methoden. Teil 2 (2. Aufl.). Wien: Ludwig Boltzmann Institut für Health Technology Assessment 2009 [cited 20.1.2016]. Available from: http://eprints.hta.lbg.ac.at/713/3/HTA-Projektbericht_06_(2.Auflage).pdf.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Results from randomised controlled trials of HGNS for moderate-to-severe OSA

Author, year	Woodson et al. 2014 [14]	Smart et al. 2013 [15]
Country	Germany, United States, The Netherlands	Australia
Study ID	NCT01161420 (randomised subset)	NCT01446601[20]
Sponsor	Inspire Medical, Inc.	Apnex Medical, Inc.
Intervention/Product	Inspire® Upper Airway Stimulation (UAS) System	HNS/HGNS®
Comparator	HNS off for one week and until 13-mo PSG was performed, then therapy resumed	Device activated 7 mo post-implantation
Study design	Randomised Controlled Withdrawal Study	RCT (allocated 2:1)
Number of pts	46	21
Inclusion criteria	1. Diagnosis of moderate-to-severe obstructive sleep apnea with difficulty accepting or adhering to CPAP treatment. 2. BMI ≤32.0 3.AHI ≥20-50/h 4. Central or mixed sleep-disordered breathing events <25% of all apnea and hypopnea episodes 5. Non-supine AHI >10/h 6. No complete concentric collapse at the retropalatal airway observed in DISE Consecutive cohort of treatment responders (at least 50% reduction of AHI from baseline and AHI less than 20 events/hr), 12 months after device implantation	Usual treatment options failed AHI 20-80
Age of patients (yrs), Mean (SD)	ON group 57.1 (10.0); OFF group 52.7 (10.4)	54.3 (1.7)
Body mass index (kg/m2), Mean (SD)	ON group 28.4 (2.4); OFF group 27.3 (2.4)	NR
Sex	ON group 22 male, 1 female; OFF group 19 male, 4 female	4 female, 17 male
Follow-up (months)	6 months (after 12 mo followed from Strollo 2014, consecutive responders entered RCT)	6 months
Loss to follow-up, n (%)	0 (0)	0 (0)

[20] Study terminated following a negative interim analysis

Author, year	Woodson et al. 2014 [14]	Smart et al. 2013 [15]
Outcomes		
Efficacy (Hypoglossal nerve stimulation vs no stimulation)		
AHI, Mean (SD)	ON group: Baseline (at 12 mo): 7.2 (5.0); after 1 week: 8.9 (9.1); Δ = 1.7 (6.4) OFF group: Baseline (at 12 mo): 7.6 (4.0); after 1 week [device off]: 25.8 (16.2); Δ = 18.2 (15.6) Difference between groups after 1 week: -16.9 (95% CI -24.7, -9.0) p<0.001 ON group: 18 mo: 9.6 (11.3); OFF group: 18 mo [device on]: 10.7 (7.3) Difference between groups after 18 mo: -1.1 (95% CI -6.9, 4.7) p= 0.85	Device active: Baseline: 34.1 (3.5); 6 mo: 22.1 (5.2) Control: Baseline: 40.9 (6.5); 6 mo: 29.7 (6.2) Difference between groups at 6 months: n.s.
Oxygen Desaturation Index, Mean (SD)	ON group: Baseline (at 12 mo): 6.3 (5.4); after 1 week: 8.0 (8.9); Δ = 1.6 (5.8) OFF group: Baseline (at 12 mo): 6.0 (3.7); after 1 week [device off]: 23.0 (15.6); Δ = 17.0 (14.5) Difference between groups after 1 week: -15.1 (95% CI -22.7, -7.5) p<0.001 ON group: 18 mo: 8.6 (11.0); OFF group: 18 mo [device on]: 9.1 (6.1) Difference between groups after 18 mo: -0.5 (95% CI -5.9, 5.0) p=0.86	Device active: Baseline: 10.8 (2.5); 6 mo: 11.4 (4.1) Control: Baseline: 22.2 (4.3); 6 mo: 19.5 (5.2) Difference between groups at 6 months: n.s. Difference at baseline between groups p<0.05
Functional Outcome of Sleep Questionnaire, Mean (SD)[21]	ON group: Baseline (at 12 mo): 17.9 (2.9); after 1 week: 17.9 (2.9); Δ = 0.0 (1.0) OFF group: Baseline (at 12 mo): 17.0 (3.5); after 1 week [device off]: 15.0 (4.0); Δ = 2.3 (3.0) Difference between groups after 1 week: 2.9 (95% CI 0.8, 5.0) p= 0.008 ON group: 18 mo: 18.0 (2.9); OFF group: 18 mo [device on]: 17.1 (2.9) Difference between groups after 18 mo: 0.9 (95% CI -0.8, 2.6) p=0.29	n.r.
Epworth Sleepiness Scale, Mean (SD)[22]	ON group: Baseline (at 12 mo): 5.9 (3.4); after 1 week: 5.6 (3.9); Δ = 0.3 (1.8) OFF group: Baseline (at 12 mo): 6.9 (4.6); after 1 week [device off]: 10.0 (6.0); Δ = -3.8 (4.6) Difference between groups after 1 week: -4.5 (95% CI -7.5, -1.4) p=0.005 ON group: 18 mo: 6.0 (3.7); OFF group: 18 mo [device on]: 8.0 (4.4) Difference between groups after 18 mo: -2.0 (95%CI -4.5, 0.4) p=0.09	Device active: Baseline: 11.1 (1.6); 6 mo: 9.8 (1.0) Control: Baseline: 13.6 (2.0); 6 mo: 14.1 (2.5) Difference between groups at 6 months: n.s.

SD = Standard deviation, mo = months, yrs = years, n.r. = not reported; n.s. = statistically not significant; hr = hour;

[21] Functional Outcome of Sleep Questionnaire score range from 5 to 20, where a higher score implies better subjective sleep quality (2.0 points increase is considered a minimally important difference)

[22] Epworth Sleepiness Scale range from 0-24, where a higher score indicates an increased risk to fall asleep during daily activities. Minimally important difference is not defined, but experts consider a 1 point change in ESS to be clinically significant

Table A-2a: Results from single-arm studies of HGNS for moderate-to-severe OSA (Apnex HNS/HGNS®)

Author, year	Eastwood et al. 2011 [19]	Kezirian et al. 2014 [20]
Study ID	NCT01186926	NCT01186926 NCT01211444
Country	Australia, United States	Australia, United States
Sponsor	Apnex Medical, Inc.	Apnex Medical, Inc.
Intervention/Product	HNS/HGNS®	HNS/HGNS®.
Comparator	No	No
Study design	Multicenter, prospective single-arm interventional trial	Multicenter, single arm, open label study
Number of pts	21	32 (including 21 pts of Eastwood et al.)
Inclusion criteria	1. Age from 21 to 70 years old. 2. Diagnosis of moderate-to-severe OSA with failure of CPAP treatment. 3. BMI ≤40kg/m2. 4. AHI 20-100/h (≥15/h in NREM), ≥80% hypopneas as a proportion of the sum of apnea and hypopnea events.	1. Age from 21 to 70 years old. 2. Diagnosis of moderate-to-severe OSA with failure of CPAP treatment. 3. BMI ≤ 40kg/m2. 4. AHI 20-100/h (≥15/h in NREM), ≥80% hypopneas as a proportion of the sum of apnea and hypopnea events.
Age of patients (yrs), Mean (SD)	53.6 (9.2)	52.4 (9.4)
Body mass index (kg/m2), Mean (SD)	32.7 (3.6)	32.4 (3.6)
Sex	14 male, 7 female	20 male, 11 female
Follow-up (months)	6	12
Loss to follow-up, n (%)	2 (10)	1 (3)
Safety-related Outcomes		
Time since implantation	6 months	12 months
Serious adverse events§, n (%)	3/21* (14)	9/31* (29)
Death	0	0
System explants	2 (1 elective removal before activation, 1 due to infection)	4 (1 elective removal before activation, 1 device infection, 2 insufficient objective and subjective effectiveness)
Infection	1	1
Cuff dislodgement	1	2
Spinal accessory nerve damage	1	1
Readmission to hospital for psychological disturbance	0	1
Serious adverse device effects (SADE), n(%)	2/21 (10)	3/31 (10)
Adverse events§, n (%)	66 events¥; 12/21* (57) £	Number of events n.r.; 22/31* (71) £

*§ System (device or therapy) or procedure-related * Totals refer to number of patients with an event (i.e., one subject may have had >1 event of a given severity); ¥ double counting of events possible because of unclear reporting; £ underreporting of patients possible because of unclear reporting; SD = Standard deviation; pts = patients; yrs = years*

Table A-2b: Results from single-arm studies of HGNS for moderate-to-severe OSA (Inspire® Upper Airway Stimulation System)

Author, year	Strollo et al. 2014 [16]	Strollo et al. 2015 [17]	Woodson et al. 2016 [18]	Van de Heyning et al. 2012 [72]
Study ID	NCT01161420			n.r.
Country	Germany, Belgium, United States, The Netherlands	Germany, Belgium, United States, The Netherlands	Germany, Belgium, United States, The Netherlands	USA, Germany, Belgium, Israel
Sponsor	Inspire Medical, Inc.	Inspire Medical, Inc.	Inspire Medical, Inc.	Inspire Medical, Inc.
Intervention/Product	Inspire® Upper Airway Stimulation System	Inspire® Upper Airway Stimulation System	Inspire® Upper Airway Stimulation System	HNS/Inspire II Upper Airway Stimulation (UAS) System
Comparator	No	No	No	No
Study design	Multicenter, prospective, single-group, cohort design	Multicenter, prospective, single-group, cohort design	Multicenter, prospective, single-group, cohort design	Multicenter, prospective single arm study
Number of pts	126	126	126	31 (Part 1: 22; 2 excluded; Part 2: 9; 1 excluded)
Inclusion criteria	1. Diagnosis of moderate-to-severe obstructive sleep apnea with difficulty accepting or adhering to CPAP treatment. 2. BMI ≤32.0 3. AHI ≥20-50/h 4. Central or mixed sleep-disordered breathing events <25% of all apnea and hypopnea episodes 5. Non-supine AHI >10/h 6. No complete concentric collapse at the retropalatal airway observed in DISE	1. Diagnosis of moderate-to-severe obstructive sleep apnea with difficulty accepting or adhering to CPAP treatment. 2. BMI ≤32.0 3. AHI ≥20-50/h 4. Central or mixed sleep-disordered breathing events <25% of all apnea and hypopnea episodes 5. Non-supine AHI >10/h 6. No complete concentric collapse at the retropalatal airway observed in DISE	1. Diagnosis of moderate-to-severe obstructive sleep apnea with difficulty accepting or adhering to CPAP treatment. 2. BMI ≤32.0 3. AHI ≥20-50/h 4. Central or mixed sleep-disordered breathing events <25% of all apnea and hypopnea episodes 5. Non-supine AHI >10/h 6. No complete concentric collapse at the retropalatal airway observed in DISE	Part 1: moderate-to-severe OSA, failed or were intolerant of CPAP treatment BMI <35 kg/m2 AHI ≥25/h Part 2: moderate-to-severe OSA, failed or were intolerant of CPAP treatment, prospectively selected based on predictors of therapy response in Part 1 BMI ≤32 kg/m2 AHI 20-50/h Pts. without complete concentric collapse at the level of soft palate (determined by DISE)
Age of patients (yrs), Mean (SD)	54.5 (10.2)	54.5 (10.2)	54.5 (10.2)	Part 1: 55.7 (8.1) Part 2: 53.6 (11.9)
Body mass index (kg/m2), Mean (SD)	28.4 (2.6)	28.4 (2.6)	28.4 (2.6)	Part 1: 55.7 (8.1) Part 2: 53.6 (11.9)
Sex	104 male, 22 female	104 male, 22 female	104 male, 22 female	Part 1: 20 male Part 2: 7 male, 1 female
Follow-up (months)	12	18	36	6
Loss to follow-up, n (%)	2/126 (1.6)	3/126 (2.3)	10/126 (8)	Part 1: 2/22 (9) Part 2: 1/9 (11)

Author, year	Strollo et al. 2014 [16]	Strollo et al. 2015 [17]	Woodson et al. 2016 [18]	Van de Heyning et al. 2012 [72]
Safety-related Outcomes				
Time since implantation (SD)	12 months	12 to 18 months	Total for an average of 40 (6) months	6 months
Serious Adverse Events (SAE), n (%)	35 events, 27/126* (21), [reported for an average of 20 months, Strollo et al. 2014 Supplementary Appendix Table S1]		n.r.	Part 1: 2/21* (10); Part 2: 1/9* (11)
Death, unrelated	2 (2)		3 (1cardiac event, 1 homicide, 1 cardiac arrest after fall)	0
Other unrelated	31 events, 23/126* (18)		n.r.	2
Serious Adverse Device Effect (SADE), n (%)	2 device revisions, 2/126* (2), [reported for an average of 20 months, Strollo et al. 2014 Supplementary Appendix Table S1]		3 events, 3/126* (2)	2/30 (7)
System explants	1 elective explant		3 (2 elective explant, 1 device-unrelated septic arthritis)	1
System (device or therapy) or procedure-related adverse events, n (%)	343 events, number of pts n.r. [Strollo et al. 2015 Table S1]	49 events, number of pts n.r. [Strollo et al. 2015 Table S1]	469 events, number of pts n.r. [Woodson et al. 2016 Supplementary Appendix Table S1]	15 events, number of pts n.r.

* *Totals refer to number of patients with an event (i.e., one subject may have had >1 event of a given severity); DISE = drug-induced sleep endoscopy; pts = patients; n.r. = not reported; SD = Standard deviation; yrs = years*

Table A-2c: Results from single-arm studies of HGNS for moderate-to-severe OSA (ImThera Aura6000™)

Author, year	Mwenge et al. 2013 [21]
Study ID	NCT01532180
Country	Belgium
Sponsor	ImThera Medical, Inc.
Intervention/Product	Aura6000TM
Comparator	No
Study design	Open-label, single-site, single-arm interventional trial
Number of pts	14
Inclusion criteria	1. Age from 25 to 70 years. 2. Refusal of CPAP treatment. 3. AHI ≥20 events/h. 4. BMI 25-40 kg/m2. 5. Modified Mallampati score from I to III[23] and palatine tonsils assessed as grade 0, 1 or 2
Age of patients (yrs), Mean (SD)	50.3 (9.6)
Body mass index (kg/m2), Mean (SD)	30.5 (3.4)
Sex	13 male, 1 female
Follow-up (months)	12
Loss to follow-up, n (%)	1/14 (7)
Safety-related Outcomes	
Time since implantation	12 months
Serious Adverse Device Effect (SADE), n (%)	3/13* (23)
Death	0
System explants (defective connector at surgery)	1/14
Broken lead, defective IPG	3/13
System (device or therapy) or procedure-related adverse events, n (%)	64 events, 14/14* (100)

* *Totals refer to number of patients with an event (i.e., one subject may have had >1 event of a given severity); IPG = implanted pulse generator; pts = patients; SD = Standard deviation; yrs = years*

[23] Modified Mallampati Scoring: Class I: Soft palate, uvula, fauces, pillars visible. Class II: Soft palate, uvula, fauces visible. Class III: Soft palate, base of uvula visible

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 LBI-HTA [73] and in the Guidelines of EUnetHTA [22].

Table A-3: Risk of bias – study level (randomised studies), see [22]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
Woodson et al. 2014	Unclear	Unclear	No	No	Yes	Yes	High[24]
Smart et al. 2013[25]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

n.a. = not applicable

Table A-4: Risk of bias – study level (case series), see [23]

IHE QA checklist: critical appraisal single-arm studies [23]	Eastwood et al. 2011, NCT01186926 [19]	Kezirian et al. 2014 NCT01186926 NCT01211444 [20]	Mwenge et al. 2013, NCT01532180 [21]	Van de Heyning et al. 2012 [72]	Strollo et al. 2014, NCT01161420 [16]	Strollo et al. 2015, NCT01161420 [17]	Woodson et al. 2016, NCT01161420 [18]
Study objective							
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study population							
2. Are the characteristics of the participants included in the study described?	Partial[26]	Partial[26]	Yes	Partial[26]	Yes	Yes	Partial[26]
3. Were the cases collected in more than one centre?	Yes	Yes	No	Yes	Yes	Yes	Yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Were participants recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

[24] No details were provided on how randomisation and allocation concealment was achieved

[25] Insufficient information available to assess the risk of bias (abstract only)

[26] Comorbidities only partially reported

IHE QA checklist: critical appraisal single-arm studies [23]	Eastwood et al. 2011, NCT01186926 [19]	Kezirian et al. 2014 NCT01186926 NCT01211444 [20]	Mwenge et al. 2013, NCT01532180 [21]	Van de Heyning et al. 2012 [72]	Strollo et al. 2014, NCT01161420 [16]	Strollo et al. 2015, NCT01161420 [17]	Woodson et al. 2016, NCT01161420 [18]
6. Did participants enter the study at similar point in the disease?	Unclear	Unclear	Yes	Unclear[27]	Yes	Yes	Unclear
Intervention and co-intervention							
7. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome measures							
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Analysis							
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results and Conclusions							
13. Was the length of follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Was the loss to follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?[28]	n/a	n/a	n/a	n/a	n/a	n/a	n/a
16. Are adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Competing interest and source of support							
18. Are both competing interest and source of support for the study reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[27] Study was conducted in 2 parts. Patients enrolled in part 1 differed in disease severity from patients in part 2.

[28] This criterion was not applicable for the relevant outcomes that were used for recommendation

Applicability table

Table A-5: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	All studies included patients with moderate-to-severe obstructive sleep apnea with difficulty accepting or adhering to CPAP treatment, respectively with failure of usual treatment options. 70% of included patients had AHI between 20 and 50 and BMI less than 32. 60% of included patients were diagnosed not having complete concentric collapse at the retropalatal airway observed in drug-induced sleep endoscopy. The inclusion criteria and the population in the studies seem to be in accordance with the intended patient population for the technology outlined in the application form. Patient characteristics included in studies may not be representative of the population affected by OSA. Both hyplossal nerve stimulation systems are approved for treatment of moderate-to-severe obstructive sleep apnea in Europe (CE marking).
Intervention	The implantation of hypoglossal nerve stimulation systems was performed using three different devices. 157 patients received Inspire® UAS System (Inspire Medical, Inc.) [14, 16-18, 72]. 53 patients received HNS/HGNS® (Apnex Medical, Inc.) [15, 19, 20] and 14 patients received Aura6000™ System (ImThera Medical, Inc.) [21]. Currently, Inspire® UAS System and Aura6000™ System are marketed by two manufacturers, HNS/HGNS® System is not available anymore. Surgical implantation of the upper-airway stimulation systems was performed by specialised otolaryngologists under general anaesthetics.
Comparators	Both RCTs used "no treatment" as comparator. Although CPAP therapy is the first line therapy in moderate-to-severe obstructive sleep apnea, a control group of therapeutic CPAP users is impractical because only patients who could not use CPAP, or who declined to do so, are the target group of the intervention.
Outcomes	Frequently reported outcomes are AHI (Apnea-hypopnea index), ODI (Oxygen desaturation index), ESS (Epworth sleepiness scale) and FOSQ (Functional outcomes of sleep questionnaire). One study assessed the short-term RCT withdrawal effect after 1 week, another RCT reported 6 months outcomes. Long-term follow-up studies with clinical relevant outcomes like cardiovascular morbidity and mortality are lacking. Regarding safety outcomes, all case series reported procedure related events, therapy related events and device related events. For the assessment of safety, according to the guidelines of medical devices on serious adverse event reporting, the reported events were categorized as serious adverse event (SAE), adverse event (AE) and serious adverse device effect (SADE). One of the case series with 126 participants reported safety outcomes up to 40 months, two case series at 6 months and two at 12 months.
Setting	With one exception, the studies were conducted in more than one country. The studies were carried out in Germany, Belgium, Israel, the Netherlands, the USA and Australia. A team of experts in sleep medicine and otolaryngologists were involved in patient recruitment, the operations were performed at otolaryngologic centres inpatiently. Study centres had an experience in sleep related disorders and in the technology used, as well as in clinical research in general. The settings of the studies reflects the clinical setting in which the technology is intended to be used in an appropriate way outlined in the application form.

List of ongoing studies

Table A-6: List of ongoing randomised controlled trials of HGNS stimulation

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT02263859 Targeted Hypoglossal Neurostimulation Study #3	141 moderate-to-severe OSA that have failed or do not tolerate PAP	Implantation of aura6000 System, therapy turned ON at the Month 1 follow-up visit.	Implantation of aura6000TM System, treatment as usual, (i.e. any non-PAP, non-surgical OSA treatment including oral appliances and positional devices being used prior to enrollment in the study) until 14 days (washout period) prior to the Month 4 visit. Therapy turned ON at the Month 4 + 1 day	Improvement in Apnea Hypopnea Index (AHI) Improvement in Oxygen Desaturation Index (ODI) Safety Analysis	May 2016	ImThera Medical, Inc.

Table A-7: List of ongoing single arm studies of HGNS stimulation

Trial ID	Title	Recruitment	Study Results	Start Date	Completion Date	Number of patients	Sponsor
NCT01796925	Targeted Hypoglossal Neurostimulation Study #2	Completed	No Results Available	February 2013	September 2014	57	ImThera Medical, Inc.
NCT02293746	Inspire® Upper Airway Stimulation (UAS) System German Post-Market Study	Active, not recruiting	No Results Available	June 2014	Estimated April 2016	60	Inspire Medical Systems, Inc.
NCT01161420	Stimulation Therapy for Apnea Reduction (Www.theSTARtrial.Com)	Active, not recruiting	Has Results	July 2010	March 2017	Enrollment 929, 126 included	Inspire Medical Systems, Inc.
NCT02413970	Inspire® Post-Approval Study/Protocol Number 2014-001	Recruiting	No Results Available	May 2015	December 2021	127	Inspire Medical Systems, Inc.
NCT02312479	Safety and Performance Study of the Nyxoah SAT System for Treating OSA	Active, not recruiting	No Results Available	December 2014	July 2016	15	Nyxoah S.A.

Literature search strategies

Search strategy for Medline via OVID

Database: Ovid MEDLINE(R) <1946 to November Week 3 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 17, 2015>, Ovid MEDLINE(R) Daily Update <November 18, 2015>, Ovid OLDMEDLINE(R) <1946 to 1965>	
Search Strategy:	
1	exp Sleep Apnea, Obstructive/(13,855)
2	exp Sleep Apnea Syndromes/(26,835)
3	sleep apn?ea*.mp. (32,570)
4	snore*.mp. (1,452)
5	snoring.mp. (5,966)
6	1 or 2 or 3 or 4 or 5 (34,626)
7	exp Cranial Nerves/(101,025)
8	exp Electric Stimulation/(120,677)
9	exp Electric Stimulation Therapy/(64,207)
10	8 or 9 (182,881)
11	7 and 10 (10,685)
12	((cranial or hypoglossal) adj10 stimulation*).mp. (970)
13	(nerve* adj10 stimulat*).mp. (47,759)
14	hypoglossal cranial nerve stimulation*.mp. (0)
15	hypo-glossal cranial nerve stimulation*.mp. (0)
16	HNS.mp. (1,102)
17	11 or 12 or 13 or 16 (54,702)
18	6 and 17 (207)
19	(((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 extract*))).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. (260,668)
20	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/not humans.sh.) (3,224,997)
21	19 or 20 (338,3575)
22	18 and 21 (42)
23	remove duplicates from 22 (36)
Search date: 18th December 2015	

Search strategy for Embase

No.	Query Results	Results	Date
#27	'sleep disordered breathing'/exp OR 'sleep apnea' OR 'sleep apneas' OR 'sleep apnoea' OR 'sleep apnoeas' OR 'snoring'/exp OR snore* OR snoring AND ('cranial nerve'/exp AND ('electrostimulation'/exp OR 'electrostimulation therapy'/exp) OR (cranial OR hypoglossal OR 'hypoglossal') NEAR/10 stimulation* OR nerve* NEAR/10 stimulat* OR hns:ab,ti) AND ('clinical trial'/de OR 'clinical trial (topic)'/de OR 'cohort analysis'/ de OR 'controlled study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'multicenter study (topic)'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de) AND 'human'/de OR ('sleep disordered breathing'/exp OR 'sleep apnea' OR 'sleep apneas' OR 'sleep apnoea' OR 'sleep apnoeas' OR 'snoring'/exp OR snore* OR snoring AND ('cranial nerve'/exp AND ('electrostimulation'/exp OR 'electrostimulation therapy'/exp) OR (cranial OR hypoglossal OR 'hypoglossal') NEAR/10 stimulation* OR nerve* NEAR/10 stimulat* OR hns:ab,ti) AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim))	135	18 Dec 2015
#26.	'sleep disordered breathing'/exp OR 'sleep apnea' OR 'sleep apneas' OR 'sleep apnoea' OR 'sleep apnoeas' OR 'snoring'/exp OR snore* OR snoring AND ('cranial nerve'/exp AND ('electrostimulation'/exp OR 'electrostimulation therapy'/exp) OR (cranial OR hypoglossal OR 'hypoglossal') NEAR/10 stimulation* OR nerve* NEAR/10 stimulat* OR hns:ab,ti) AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim)	21	18 Dec 2015
#25.	'sleep disordered breathing'/exp OR 'sleep apnea' OR 'sleep apneas' OR 'sleep apnoea' OR 'sleep apnoeas' OR 'snoring'/exp OR snore* OR snoring AND ('cranial nerve'/exp AND ('electrostimulation'/exp OR 'electrostimulation therapy'/exp) OR (cranial OR hypoglossal OR 'hypoglossal') NEAR/10 stimulation* OR nerve* NEAR/10 stimulat* OR hns:ab,ti) AND ('clinical trial'/de OR 'clinical trial (topic)'/de OR 'cohort analysis'/ de OR 'controlled study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'multicenter study (topic)'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de) AND 'human'/de	130	18 Dec 2015
#24.	'sleep disordered breathing'/exp OR 'sleep apnea' OR 'sleep apneas' OR 'sleep apnoea' OR 'sleep apnoeas' OR 'snoring'/exp OR snore* OR snoring AND ('cranial nerve'/exp AND ('electrostimulation'/exp OR 'electrostimulation therapy'/exp) OR (cranial OR hypoglossal OR 'hypoglossal') NEAR/10 stimulation* OR nerve* NEAR/10 stimulat* OR hns:ab,ti) AND ('clinical trial'/de OR 'clinical trial (topic)'/de OR 'cohort analysis'/ de OR 'controlled study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'multicenter study (topic)'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de)	169	18 Dec 2015
#23.	'sleep disordered breathing'/exp OR 'sleep apnea' OR 'sleep apneas' OR 'sleep apnoea' OR 'sleep apnoeas' OR 'snoring'/exp OR snore* OR snoring AND ('cranial nerve'/exp AND ('electrostimulation'/exp OR 'electrostimulation therapy'/exp) OR (cranial OR hypoglossal OR 'hypoglossal') NEAR/10 stimulation* OR nerve* NEAR/10 stimulat* OR hns:ab,ti)	602	18 Dec 2015
#22.	cranial nerve'/exp AND ('electrostimulation'/exp OR 'electrostimulation therapy'/exp) OR (cranial OR hypoglossal OR 'hypoglossal') NEAR/10 stimulation* OR nerve* NEAR/10 stimulat* OR hns:ab,ti	100,154	18 Dec 2015
#21.	hns:ab,ti	1,197	18 Dec 2015
#20.	'hypo-glossal cranial nerve stimulations'		18 Dec 2015
#19.	'hypoglossal cranial nerve stimulations'		18 Dec 2015
#18.	'hypo-glossal cranial nerve stimulation'		18 Dec 2015
#17.	'hypoglossal cranial nerve stimulation'		18 Dec 2015
#16.	nerve* NEAR/10 stimulat*	95,730	18 Dec 2015
#15.	(cranial OR hypoglossal OR 'hypo glossal') NEAR/10 stimulation*	1,080	18 Dec 2015
#14.	'cranial nerve'/exp AND ('electrostimulation'/exp OR 'electrostimulation therapy'/exp)	8,189	18 Dec 2015
#13.	'electrostimulation'/exp OR 'electrostimulation therapy'/exp	258,953	18 Dec 2015
#12.	electrostimulation therapy'/exp	195,462	18 Dec 2015
#11.	'electrostimulation'/exp	73,409	18 Dec 2015

No.	Query Results	Results	Date
#10.	'cranial nerve'/exp	89,666	18 Dec 2015
#9.	'sleep disordered breathing'/exp OR 'sleep apnea' OR 'sleep apneas' OR 'sleep apnoea' OR 'sleep apnoeas' OR 'snoring'/exp OR snore* OR snoring	57,541	18 Dec 2015
#8.	snoring	10,234	18 Dec 2015
#7.	snore*	2,121	18 Dec 2015
#6.	'snoring'/exp	8,773	18 Dec 2015
#5.	'sleep apnoeas'	111	18 Dec 2015
#4.	'sleep apnoea'	7,321	18 Dec 2015
#3.	'sleep apneas'	487	18 Dec 2015
#2.	'sleep apnea'	34,582	18 Dec 2015
#1.	'sleep disordered breathing'/exp	51,760	18 Dec 2015

Search strategy for CRD (DARE-NHS EED-HTA)

#### Electric nerve stimulation for Sleep Apnea	
1	MeSH DESCRIPTOR Sleep Apnea, Obstructive EXPLODE ALL TREES
2	MeSH DESCRIPTOR Sleep Apnea Syndromes EXPLODE ALL TREES
3	(sleep apn*ea*)
4	MeSH DESCRIPTOR Snoring EXPLODE ALL TREES
5	(snore*)
6	(snoring)
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	MeSH DESCRIPTOR Electric Stimulation EXPLODE ALL TREES
9	MeSH DESCRIPTOR Electric Stimulation Therapy EXPLODE ALL TREES
10	(stimulat*)
11	MeSH DESCRIPTOR Hypoglossal Nerve EXPLODE ALL TREES
12	MeSH DESCRIPTOR Cranial Nerves EXPLODE ALL TREES
13	((cranial OR hypoglossal) NEAR stimulat*)
14	((cranial OR hypo-glossal) NEAR stimulat*)
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16	#7 AND #15
7 Hits	
Search date: 18th December 2015	

Search strategy for Cochrane Library

Search Name: HNS for Sleep Apnea	
Last Saved: 21.12.2015 17:41:58	
ID	Search
#1	MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees
#2	MeSH descriptor: [Sleep Apnea Syndromes] explode all trees
#3	MeSH descriptor: [Snoring] explode all trees
#4	sleep apnea* (Word variations have been searched)
#5	sleep apnoea* (Word variations have been searched)
#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 Therapy] explode all trees
#12	#10 or #11
#13	#9 and #12
#14	(cranial or hypoglossal) near stimulation* (Word variations have been searched)
#15	nerve* near stimulat* (Word variations have been searched)
#16	hypoglossal cranial nerve stimulation* (Word variations have been searched)
#17	hypo-glossal cranial nerve stimulation* (Word variations have been searched)
#18	HNS:ti,ab,kw (Word variations have been searched)
#19	#13 or #14 or #15 or #16 or #18
#20	#8 and #19
34 Hits	

Search strategy for PubMed

PubMed Suchstring:
(((((Sleep Apnea, Obstructive[Mesh] OR Sleep Apnea Syndromes[Mesh] OR sleep apnea* OR sleep apnoea* OR snore* OR snoring[Mesh] OR snoring))) AND ((Cranial Nerves[Mesh] AND (Electric Stimulation[Mesh] OR Electric Stimulation Therapy[Mesh]) OR cranial stimulation* OR hypoglossal stimulation* OR nerve* AND stimulat* OR hypoglossal cranial nerve stimulation* OR hypo-glossal cranial nerve stimulation* OR HNS[tiab])) AND Clinical Trial[ptyp])) OR ((((Sleep Apnea, Obstructive[Mesh] OR Sleep Apnea Syndromes[Mesh] OR sleep apnea* OR sleep apnoea* OR snore* OR snoring[Mesh] OR snoring))) AND ((Cranial Nerves[Mesh] AND (Electric Stimulation[Mesh] OR Electric Stimulation Therapy[Mesh]) OR cranial stimulation* OR hypoglossal stimulation* OR nerve* AND stimulat* OR hypoglossal cranial nerve stimulation* OR hypo-glossal cranial nerve stimulation* OR HNS[tiab])) AND ((Meta-Analysis[ptyp] OR systematic[sb]))))
21 Hits
Search date: 21st December 2015