Region Västra Götaland, HTA-centrum

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Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea

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Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnoea. [Stimulering av hypoglossusnerven för behandling av obstruktiv sömnapné]

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Abbreviations

AE	Adverse Events
AHI	Apnoea/Hypopnea Index
BDI	Beck Depression Inventory
BMI	Mody Mass Index
CPAP	Continuous Positive Airway Pressure
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
GBP	Great Britain Pound
HGNS	HypoGlossal Nerve Stimulation
ICER	Incremental Cost-Effectiveness Ratio
Mean SaO2	Overnight mean oxygen saturation
MRD	Mandibular Retaining Device
NREM	Non-REM
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnoea
PAP	Positive Airway Pressure
PG	Polygraphy
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
QALY	Quality Adjusted Life Years
REM	Rapid Eye Movement sleep
SAE	Serious Adverse Event
SAQLI	Calgary Sleep Apnea Quality of life Index
UPPP	UvuloPalatoPharyngoPlasty

1. Summary of the Health Technology Assessment

Background

Obstructive sleep apnoea (OSA) is characterised by repetitive upper airway collapse during sleep and is associated with intermittent hypoxia and transient arousals. The condition is associated with excessive daytime sleepiness, cognitive dysfunction as well as increased risk of traffic accidents, hypertension, coronary artery disease and stroke. The prevalence of symptomatic OSA exceeds 2% in women and 4% in men in the age span 30-60 years. Continuous positive airway pressure, the current mainstay of therapy in OSA patients, is generally well tolerated but long-term compliance is limited and estimated to be in the order of 50%. It has been estimated that some 20% (approximately 5,000) of diagnosed OSA patients are unable to tolerate continuous positive airway pressure or any other current treatment. Approximately 100-150 of these may be suitable for hypoglossal nerve stimulation, a technique where the hypoglossal nerve is electrically stimulated causing protrusion of the tongue.

Objective

To evaluate the effectiveness and risks of hypoglossal nerve stimulation in patients with obstructive sleep apnoea refractory to continuous positive airway pressure.

Search methods and study selection criteria

Systematic searches were performed in PubMed, Embase, the Cochrane Library and a number of HTA databases. Reference lists of relevant articles were scrutinized for additional references. Studies were required to be a systematic review, a controlled study or a case series.

Main results

Seven articles met the inclusion criteria (PICO), one study including both a case series and a randomised controlled trial, and additionally six case series. In this HTA, although unconventional, the case series were included because data on the natural evolution of OSA was considered as a valid marker of no treatment or intervention.

The randomized controlled trial had a therapy withdrawal design. Also the case series, several of which were well designed, were assessed for quality using a modified previously published check list. Grading the quality of evidence was first done for the randomized controlled trial (starting at ⊕⊕⊕⊕) and then for the case series (starting at ⊕◯◯◯). Finally, a combined quality of evidence (GRADE) was defined in a consensus discussion.

No articles reported any of the critical outcomes. Hypoglossal nerve stimulation therapy significantly reduced sleep apnoea, expressed as apnoea/hypopnea index (the number of apnoeas and hypopneas events/hour sleep) and oxygen desaturation index (the number of times/hour sleep that the blood oxygen level drops by ≥4 percentage points from baseline) by approximately 50% in the randomized controlled trial and six of seven case-series (⊕⊕◯◯). Regarding symptoms and signs of OSA including Functional Outcomes of Sleep Questionnaire, Epworth Sleepiness Scale and objective sleep quality, it is uncertain whether the observed improvements correspond to established clinically meaningful effect sizes (⊕◯◯◯). Severe adverse events are rare and the most frequent procedure related complications include tongue abrasions, tongue soreness or weakness. Stimulation related discomfort was often transitional.

Concluding remarks

This report assessing the evidence for hypoglossal nerve stimulation therapy in patients with obstructive sleep apnoea refractory to continuous positive airway pressure shows that the therapy may substantially reduce important measures of OSA severity (⊕⊕◯◯). Patient selection appears to be essential to the success of therapy. Severe device-related adverse events are rare. The hypoglossal nerve stimulation treatment is expensive and further studies with long-term follow-up are needed.

2. Svensk sammanfattning – Swedish summary

Bakgrund

Obstruktiv sömnapné (OSA) karakteriseras av upprepad kollaps av övre luftvägarna under sömn och är förknippat med intermittent hypoxi och ökad vakenhetsgrad. Tillståndet är förknippat med uttalad sömnighet dagtid, kognitiv dysfunktion liksom en ökad risk för trafikolyckor, hypertoni, ischemisk hjärtsjukdom och stroke. Prevalensen av symtomgivande sömnapné överstiger 2% hos kvinnor och 4% hos män i åldrarna 30-60 år. Kontinuerlig övertrycksbehandling, den viktigaste terapiformen vid symtomgivande OSA, tolereras i regel väl men långsiktig följsamhet till behandlingen är något begränsad och anges till cirka 50%. Det har uppskattats att cirka 20% (cirka 5 000) av diagnosticerade symtomatiska OSA-patienter ej tolererar kontinuerlig övertrycksbehandling eller någon annan idag tillgänglig terapi. Uppskattningsvis 100 – 150 av dessa skulle kunna vara tillgängliga för hypoglossusnervstimulering, en metod som kan lindra OSA genom att tungan förskjuts framåt så att övre luftvägarna vidgas.

Syfte

Att utvärdera effektiviteten av och risker med stimulering av hypoglossusnervstimulering hos patienter med OSA som är refraktär till kontinuerlig övertrycksbehandling.

Resultat

Litteratursökningen identifierade sju artiklar som uppfyllde uppställda inklusionskriterier, varav en artikel inkluderade både en randomiserad kontrollerad studie och en fallserie; utöver denna artikel fanns sex fallserier. Trots att det är okonventionellt inkluderades även fallserier i bedömningen av resultaten och det vetenskapliga underlaget, eftersom publicerade data om naturalförloppet för OSA ansågs väl återspegla utebliven behandling. Den randomiserade kliniska studien hade en så kallad therapy withdrawal design och granskades med checklista. Även fallserierna, av vilka flera var prospektiva och väldesignade, granskades kvalitetsmässigt med en modifierad tidigare publicerad checklista för fallserier. Bedömning av evidensstyrkan enligt GRADE gjordes först för den randomiserade studien (start på ⊕⊕⊕⊕) och sedan för fallserierna (start på ⊕◯◯◯). Till sist gjordes i en konsensusdiskussion en sammanvägd bedömning av evidensstyrkan (GRADE).

Inga artiklar rapporterade något av de kritiska utfallsmåtten. Hypoglossusnervstimulering reducerade signifikant svårighetsgraden av OSA. Detta mättes med apne/hypopne index (antal andningsuppehåll/andningssviktsepisoder/h sömn) och oxygen desaturation index (antal gånger/h sömn som syrgashalten i blodet sjunker med mer än fyra procentenheter), med cirka 50% i den randomiserade studien och i sex av sju fallserier (⊕⊕◯◯). I den sjunde fallserien reducerades svårighetsgraden av OSA när enbart patienter som idag behandlas med hypoglossusnervstimulering inkluderades. Sömnkvalitet studerades enbart i fallserier och det är osäkert huruvida hypoglossusnervstimulering ger kliniskt meningsfull förbättring av sömnkvaliteten (⊕◯◯◯). De vanligaste rapporterade biverkningarna inkluderade sårighet på tungan eller tungsvaghet. Dessa obehag var ofta relativt snabbt övergående.

Sammanfattande bedömning

Denna rapport utvärderar hypoglossusnervstimulering för patienter med OSA som är refraktär till kontinuerlig övertrycksbehandling. Inga av de kritiska utfallen är studerade, men etablerade mått på svårighetsgraden av OSA förbättras avsevärt (⊕⊕◯◯). Patientselektion förefaller vara viktig för att nå framgång med metoden. Allvarliga biverkningar är ovanliga, men metoden är kostsam och det behövs ytterligare studier med långtidsuppföljning.

The above summaries were written by HTA-centrum and approved by the Regional board for quality assurance of activity-based HTA. HTA-centrum, Region Västra Götaland, Sweden has the task to make statements on HTA reports carried out in VGR. The English summary is a concise summary of similar outline as the summaries in the Cochrane systematic reviews. The Swedish summary addresses the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report, and is ended with a final statement/concluding remark from HTA-centrum.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 2015-03-25

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Summary of findings

Hypoglossal nerve stimulation for treatment of obstructive sleep apnea

Outcome variable	Design Number of studies and (patients)	Relative effect	Absolute effect	Certainty of evidence GRADE
Electrical hypoglossal nerve stimulation vs. electrical hypoglossal nerve stimulator off				
AHI	RCT 1 (n=46)[1]	11-fold in favour for intervention	I: Baseline: 7.2 events/h, at 1 week: 8.8 events/h ΔAHI = 1.7 events/h C: Baseline: 7.6 events/h, at 1 week: 25.8 events/h ΔAHI = 18.2 events/h p<0.001	Combined GRADE: ⊕⊕◯◯ Low [2]
	Case-series 7 (n=231)	NA	NA	
ODI	RCT 1 (n=46)[1]	10-fold in favour for intervention	I: Baseline: 6.3/h, at 1 week: 8.0/h ΔODI = 1.7 C: Baseline: 6.0/h, at 1 week: 23.0/h ΔODI = 17.0 p<0.001	Combined GRADE: ⊕⊕◯◯ Low [2]
	Case-series 6 (n=224)	NA	NA	
ESS	Case-series 6 (n=224)	NA	NA	⊕◯◯◯ Very low [2]
FOSQ	Case-series 5 (n=210)	NA	NA	⊕◯◯◯ Very low [2]
Objective sleep quality (EEG)	Case-series 7 (n=231)	NA	NA	⊕◯◯◯ Very low [2]

High quality of evidence = ⊕⊕⊕⊕. Moderate quality of evidence = ⊕⊕⊕◯. Low quality of evidence = ⊕⊕◯◯. Very low quality of evidence = ⊕◯◯◯.

AHI=Apnoea/Hypopnea Index (i.e. the number of apnoeas and hypopneas events per hour of sleep, where AHI >30 indicates severe OSA, and AHI 15-30 indicates moderate OSA), ESS=Epworth Sleepiness Scale, FOSQ=Functional Outcomes of Sleep Questionnaire, ODI= Oxygen Desaturation Index (i.e. the number of times per hour of sleep that the blood oxygen level drops by ≥4 percentage points from baseline).

[1] Included also in the case series.

[2] For all outcomes the RCT was downgraded one step for serious indirectness (responders) and one step for some study limitations and uncertainty regarding precision and publication bias. In the case series there were also variations in degree of OSA severity among the patients. For the outcomes ESS, FOSQ, and objective sleep quality (EEG), there were serious study limitations in the case series.

3. Participants in the project

The question was posed by
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Conflicts of interest for the proposer or any of the participants in the HTA group
None declared.

Project time
HTA was accomplished during the period of 2014-11-19 - 2015-03-25.
Literature searches were made in November 2014

4. Disease/disorder of interest

Obstructive sleep apnoea and its degree of severity

Obstructive sleep apnoea (OSA), a condition characterized by repetitive upper airway collapse during sleep is associated with intermittent hypoxia and transient arousals. The condition is associated with excessive daytime sleepiness, cognitive dysfunction as well as increased risk of traffic accidents (Olaithe et al., 2013). Cardiovascular sequels, mainly hypertension (Grote et al., 1999) coronary artery disease (Peker, 2006) and stroke (Redline et al., 2010), are overrepresented and OSA has been labelled as the most common modifiable cause of hypertension (Parati et al., 2012).

The detailed pathophysiological link(s) between OSA and comorbidities remains unclear. Apnoea induced hypoxia/reoxygenation leads to activation of inflammatory mediators and the sympathetic nervous system, altered coagulation and vascular endothelial dysfunction (Hedner et al., 1988, Carlson et al., 1996). There is evidence suggesting that autonomic nervous hyperactivity caused by the sleep fragmentation in OSA is an independent contributor to this process (Hedner et al., 1988).

Sleep is associated with a marked unloading of the autonomic system. We have previously shown that sleep apnoea events induce sympathetic-medicated vasoconstriction that can be mirrored by finger pulse wave amplitude attenuation (Grote et al., 2003). The magnitude of nocturnal pulse wave attenuation was linked to daytime blood pressure (Zou et al., 2009). Sleep in itself was associated with reduced sympathetic outflow and increased parasympathetic drive derived in heart rate variability (HRV) analysis.

Prevalence and incidence of obstructive sleep apnoea

The prevalence of symptomatic OSA exceeds 2 % in women and 4 % in men in the age span 30-60 years and non-symptomatic OSA is 3-5 times as common in the population (Young et al., 1993).

OSA is not homogeneously distributed across the age span but the exact natural evolution of the disorder is only partly known from follow-up of clinical cohorts and populations. Available data suggest a slow progress of the disorder at least until the age of retirement. For instance a 17 months follow-up of 55 patients with a mean age of 55.8 years demonstrated a mean increase of OSA severity with time. Body weight was unchanged. Thirty patients worsened, 16 remained unchanged and only nine improved (Pendlebury et al., 1997). Similar prospective studies with shorter follow-up demonstrate only marginal changes in OSA across time periods of 6 months or less. Comorbid conditions like obesity may determine a considerable proportion of OSA morbidity in the middle-aged population as well as in the elderly. Weight gain, however, in OSA patients is moderate over time. With respect to heterogeneity of the OSA phenotype there is no evidence to suggest that weight gain in patients with OSA differs markedly from age matched controls of the general population.

Present treatment of obstructive sleep apnoea

Continuous positive airway pressure (CPAP) constitutes the current mainstay of therapy in OSA. The airway pressure leads to splinting of the upper airway obstruction. CPAP has been refined in several aspects, to provide an optimised upper airway pressure during different stages of sleep. Therapy is generally well tolerated but long-term compliance is limited and estimated to be in the order of 50 % (Sanchez-de-la-Torre et al., 2015). Prescription of CPAP in Sweden is subsidised by the Swedish health care system and typically restricted to a limited amount of hospitals in each health care region.

In Sweden during recent years, there has been a sharp increase in the number of prescribed intraoral mandibular retaining devices (MRD) which is an appliance constructed by dentists that protrudes the mandible forward, aiming to prevent or minimize upper airway collapse during sleep. This increase reflects an international trend based on improved treatment results of these devices. Effectiveness is undisputed but limited to a subpopulation of OSA sufferers. There is data suggesting that most major treatment effects reached by CPAP like improvement of daytime sleepiness and sleep quality also may be obtained after treatment with MRD (Vanderveken et al., 2013).

Several surgical methods including uvulopalatopharyngoplasty (UPPP), tonsillectomy and nasal surgery are practised but in a limited extent at a limited number of Ear-nose and throat clinics in Sweden. A recent randomised study demonstrated a similar effect on sleep quality by OSA as that of MRD, in a selected group of patients with mild to moderate severity of the disease (Browald et al., 2013).

Number of patients per year who undergo current treatment regimen

Approximately 40-50,000 new patients undergo diagnostic work-up for OSA in Sweden each year. The annual volume of patients treated by CPAP has been estimated to 15,000 distributed across approximately 40-50 prescribers in Sweden. It is estimated that a similar annual amount of MRDs are constructed by >200 dentists. The total volume of OSA patients with a prescribed CPAP treatment has been estimated to 100,000 in Sweden. CPAP treatment is associated with annual exchange of consumables such as mask and tubing. A CPAP device has a durability of five to eight years. MRDs are typically exchanged every four to five years and the financial models for these consumables vary between the various health care regions.

The normal pathway of a patient through the health care system

The absolute majority of patients with suspected OSA are referred to sleep units by primary care physicians. The recommended diagnostic investigation involves ambulatory 8-channel polygraphy recording which may be performed in the patient's home or in the hospital. The work-up also includes routine clinical assessment by the physician. This visit should also include anthropometric measures, a case history, social history including occupational background as well as questionnaire-based information, most commonly the Epworth Sleepiness Scale (ESS) score. The patient will be allocated to therapy based on the observed severity of the disease in combination with specific findings in the clinical assessment. For severe OSA (AHI >30) CPAP therapy is usually employed. Moderate OSA (AHI 15-30) may typically render CPAP, MRD or surgical treatment. For mild OSA without significant comorbidity, active treatment is not always instituted. However, specific circumstances, including social stigmatisation and the presence of daytime hypersomnolence may be indications for active treatment also in cases with very mild sleep apnoea. This is particularly important in patients with occupations where sleepiness is associated with significant risks.

Actual waiting time for medical assessment/treatment

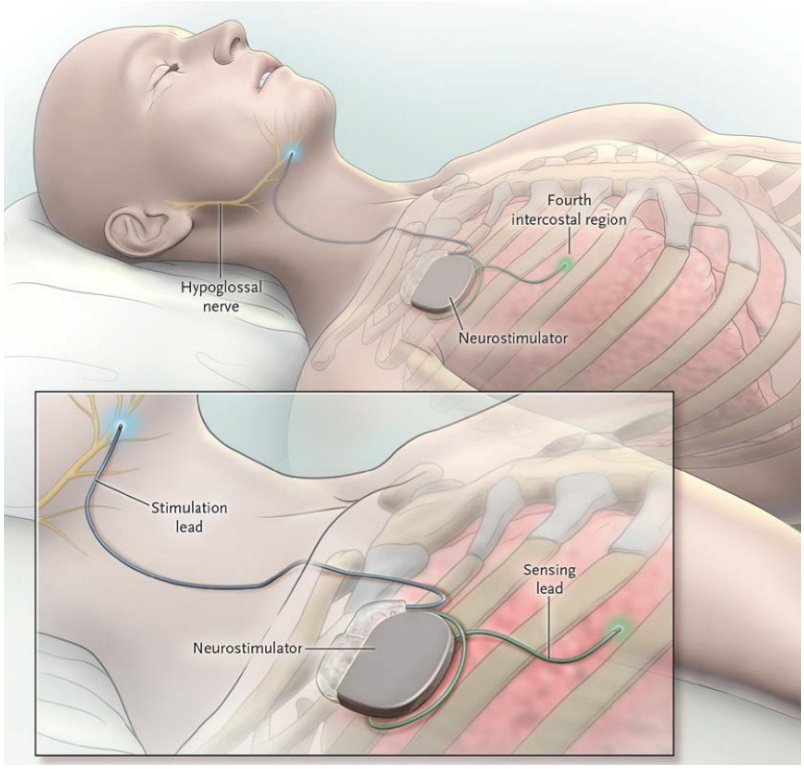
The influx of new patients to the various sleep units in Sweden appears to gradually increase. Local statistics at Sahlgrenska University Hospital, Gothenburg suggest that the annual increase is in the order of 2-3% while the mean severity of disease among referred patients had changed only marginally. Once referred the mean current time delay to diagnosis varies considerably between different centres. For instance, the range in Sweden was between 40 and 330 days according to data from the national SESAR (Swedish Sleep Apnoea Registry) data published in 2015. The average time in patients with mild OSA (AHI 5-15) was 161 days, in those with moderate OSA (AHI 15-30) 146 days and 124 days in those with severe disorder (AHI>30).

Following diagnosis most patients receive CPAP within 3 months although waiting times may be shorter at some centres. Similar conditions apply for surgical intervention. Waiting times for intraoral devices is generally shorter (2- 4 weeks).

5. Present Health Technology

Hypoglossal nerve stimulation for treatment of obstructive sleep apnoea

The HGNS implant consists of a stimulation electrode surgically placed on the hypoglossal nerve in order to recruit tongue protrusion motion. A sensing lead, connected to the impulse generator, is placed between the internal and external intercostal muscles to detect ventilatory effort thereby initiating the nerve stimulation during inspiration. The neural stimulator is surgically placed in the right ipsilateral mid-infraclavicular region.



The potential value of hypoglossal nerve stimulation

The failure rate of CPAP is in the order of 40 % in patients with moderate OSA. Similar failure rates are observed for intraoral devices. The main reasons for therapy failure include non-acceptance, side effects and/or inefficacy. Only a minority of these patients may be treated with conventional surgical (UPPP) procedures suggesting that approximately 15-20% of these patients remain untreated. Uncontrolled follow-up studies suggest that untreated OSA leads to increased cardiovascular morbidity and mortality as well as increased frequency of work and traffic related accidents. Novel treatments inducing substantial reduction of OSA and improving associated daytime symptoms provide a possibility to treat at a part of this subgroup of currently untreated patients.

The central question for the current HTA project

Is electrical hypoglossal nerve stimulation, compared with no or other treatment or electrical hypoglossal nerve stimulator off, effective in reducing morbidity, mortality, severity of OSA and in improving health related quality of life and sleep quality in patients with obstructive sleep apnoea not accepting or tolerating CPAP treatment?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

P Adults with OSA (Obstructive Sleep Apnoea) not accepting or tolerating CPAP treatment

I Electrical hypoglossus nerve stimulation

C No treatment
Other treatment
Electrical hypoglossus nerve stimulator off

O Critical for decision making

Cardiovascular morbidity
Mortality
Traffic accidents

Important (but not critical) for decision making

AHI (Apnoea-hypopnea index)
ODI (Oxygen desaturation index)
ESS (Epworth sleepiness scale)
HRQL (Health related quality of life)
FOSQ (Functional outcomes of sleep questionnaire)
Hypertension
Quality of sleep

Not important for decision making

6. Review of Certainty of Evidence

Search strategy, study selection and references (Appendix 1)

During November 2014 two librarians (UWA, AL) performed systematic searches in PubMed, Embase, the Cochrane Library, and a number of HTA-databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 1. The librarians conducted the literature searches, selected studies and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to the HTA project group, who read the articles independently and then decided in a consensus meeting which articles that should be included.

The literature search identified a total of 207 articles (after removal of duplicates). The librarians excluded 186 articles after reading the abstracts. Another nine articles were excluded by the librarians after reading the articles in full text. The remaining 12 articles were sent to the participants of the HTA project group, and seven were finally included in the report (Appendix 2). One of the included articles was a randomized controlled trial (RCT), and has been critically appraised using modified checklists from SBU (Swedish Council on Health Technology Assessment). Six of the articles were case series that were critically appraised using a slightly modified previously published checklist for case series (Guo et al., 2013). Excluded articles are listed in Appendix 3. The certainty of evidence was rated according to the GRADE system.

Appendix 2 -Included studies – design and patient characteristics
Appendix 3 - Excluded articles
Appendix 4 - Outcome tables
Appendix 5 – Ongoing research

Present knowledge of hypoglossal nerve stimulation for treatment of patients with obstructive sleep apnoea not accepting or tolerating continuous positive airway pressure

General comments

The systematic literature search identified one RCT (n=46) with therapy withdrawal design, and seven case-series. The total number of included patients was 231. The case series by Strollo et al. (2014) and Woodson et al. (2014), contained the same patients but with different follow-up times. Most case-series were relatively small, ranging from eight to 126 individuals. None of the outcomes 'critical for decision making' (cardiovascular morbidity or mortality or traffic accident) were reported. The 'important but not critical for decision-making' outcomes; AHI, ODI, ESS, FOSQ, and objective quality of sleep were reported.

Rationale for using case series

Although unconventional, the case series were included into the current HTA because data on the natural evolution of OSA was considered as a valid marker of no treatment or intervention. There is neither clinical experience nor published data suggesting that CPAP resistant OSA patients improve spontaneously within six to twelve months (or in long-term). The natural course of the OSA disorder has been investigated only in a few studies, of which the most relevant included 55 previously untreated individuals (Pendlebury et al., 1997). The progression of OSA had a tendency to worsen over time (also in presence of weight reduction) and the AHI (Apnoea/Hypopnea Index, i.e. the number of apnoeas and hypopneas events per hour of sleep) increase ranged from 21.8 to 33.4 (53 %), which was uncorrelated to BMI changes. Only 9 out of 55 patients improved their AHI during a mean of 50 weeks after the first measurement, and 4 out of these improved their AHI >50%, corresponding to the responder definition in several of the studies included in this HTA.

The case-series were evaluated for quality of evidence using a previously published checklist for case-series (Guo et al., 2013), modified by HTA-centrum Region Västra Götaland. The certainty of evidence was defined in the first step by grading the RCT, and in a second step the case series were graded. Finally, a combined grading of the RCT and the case series was performed in a consensus discussion.

Outcomes 'critical for decision making'

<u>Cardiovascular morbidity, mortality, traffic accidents</u>

There were no studies addressing these outcomes.

Outcomes 'important (but not critical) for decision making'

<u>Apnoea/Hypopnea Index (AHI) (Appendix 4:1)</u>

AHI (i.e. the number of apnoeas and hypopneas events per hour of sleep) was reported in the RCT and in all case-series. In the RCT the one week therapy withdrawal period after one year among responders resulted in a mean AHI increase from 7.2 to 8.9 within one week in the continued treatment ('on') group compared with an increase from 7.6 to 25.8 in the therapy withdrawal ('off') group ($p<0.001$). The seven case series reported an approximate 50% reduction in AHI on HGNS treatment over different follow-up periods, which in three of the case series ranged from 44 % to 54 % at twelve months follow-up. Mean AHI was significantly reduced in response to HGNS across all but one small case series, which was conducted before the present selection criteria were defined. In the latter case series, there was a significantly reduced AHI in a responder group.

Conclusion: HGNS may substantially reduce AHI in adults with obstructive sleep apnoea not accepting or tolerating CPAP treatment. Low certainty of evidence (⊕⊕◯◯).

Oxygen Desaturation Index (ODI) (Appendix 4:2)

Oxygen Desaturation Index (i.e. the number of times per hour of sleep that the blood oxygen level drops by ≥4 percentage points from baseline) was reported in the RCT and in all case series. In the RCT the therapy withdrawal after one year among the responders resulted in a mean worsening from 6.3 to 8.0 within one week in the continued treatment ('on') group versus from 6.0 to 23.0 in the therapy withdrawal ('off') group ($p<0.001$). The seven case series reported an approximate 50% ODI reduction over different follow-up periods, which in three of the case series ranged from 25 % to 52 % at 12 months follow-up. Mean ODI was reduced in response to HGNS in all but one small study, which was conducted before the present selection criteria were defined.

Conclusion: HGNS may substantially reduce ODI in adults with obstructive sleep apnoea not accepting or tolerating CPAP treatment. Low certainty of evidence (⊕⊕◯◯).

Epworth Sleepiness Scale (ESS) (Appendix 4:4)

There was no data on ESS in the RCT. ESS was reported in six case series. The mean ESS score decreased by approximately four units in response to HGNS in five of the six studies. A four unit improvement of the ESS corresponds approximately to the effect obtained by CPAP in patients with moderate-to-severe sleep apnoea.

Conclusion: It is uncertain whether HGNS affects ESS in adults with obstructive sleep apnoea not accepting or tolerating CPAP treatment. Very low certainty of evidence (⊕◯◯◯).

Functional Outcomes of Sleep Questionnaire (FOSQ) (Appendix 4:4)

There was no data on FOSQ in the RCT. FOSQ was reported in five case series. Mean FOSQ score was increased by more than two units, considered as a minimally important clinical difference, in response to HGNS in four of the five studies.

Conclusion: It is uncertain whether HGNS affects FOSQ in adults with obstructive sleep apnoea not accepting or tolerating CPAP treatment. Very low certainty of evidence (⊕◯◯◯).

Objective sleep quality (EEG) (Appendix 4:5)

Sleep staging was reported in seven case series. Deep sleep was increased in one of the seven studies while REM sleep increased in two and decreased in one study. Arousal index, reported in six studies, was reduced by approximately 50% in five of the six studies.

Conclusion: It is uncertain whether HGNS results in any difference in objective sleep quality (EEG) in adults with obstructive sleep apnoea not accepting or tolerating CPAP treatment. Very low certainty of evidence (⊕◯◯◯).

HRQoL (health related quality of life)

There were no studies addressing this outcome.

Hypertension

There were no studies addressing this outcome.

Complications (Appendix 4:6)

The most prominent treatment related complications included tongue abrasions, tongue soreness or weakness. Stimulation related discomfort was often transitional. In general, HGNS related side effects differed considerably between the studies and appeared to depend on the exact HGNS technique applied. Early studies evaluated prototype devices with technical limitations and with treatment failure rates varying between 30 and 100%. In the most recent, and largest, study there were less than 2% technical adverse events reported. Side effects reported in studies were procedure-, device- or study related. Typical procedure related side effects were wound infections while device related side effects included electrode fracture and lead dislodgement, and 88% of the reported events were observed within 30 days of the surgical procedure. Two deaths, classified as unrelated to the HGNS technique, were reported.

7. Ethical consequences

The available documentation demonstrates a positive response to treatment in most patients but the characteristics of responders are incompletely known. There are ethical aspects regarding introduction of an expensive new technology with only low and very low certainty of evidence regarding patient benefit and lack of long-term follow-up regarding treatment effects and complications. The long-term results need to be better defined. The technique is expensive and there is a risk of resource displacement.

8. Organisation

When HGNS can be put into practice

The technology is duly evaluated by regulatory authorities and is already in clinical use elsewhere in Europe and the US. The introduction of the technology in the Nordic countries starts during the spring 2015. One surgical team in each country (Sweden, Norway, Finland) has been trained in the diagnostic and therapeutic procedures. Additional training is needed for the sleep laboratory personal at each centre.

HGNS use in Region Västra Götaland

Not used.

Consequences for the hospital staff due to this new health technology

The technology will initially be operated by a limited group of experts and the specific aspects of the HGNS will gradually be spread to other co-workers. Application of the HGNS device will require a more extensive clinical work-up for diagnostic purposes compared with the current situation. However, the anticipated volumes of new, implanted devices is initially expected to be low (<5-10 cases annually).

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

It is advised that the HGNS implants are initially restricted to a limited number of centres in Sweden in order to optimize the gathering of clinical experience based on higher volumes of cases.

Medical societies or health authorities that recommend hypoglossal nerve stimulation for treatment of obstructive sleep apnoea

No.

9. Economy aspects

Present costs of currently used technologies

The annual treatment cost in Sweden for OSA is estimated to 150 MSEK for CPAP and some 120MSEK for MRDs. In addition there is an annual cost of consumables corresponding to approximately 50 MSEK. The volumes (and costs) for surgical interventions are limited and hard to estimate. Less than 200 patients per year are likely to undergo surgery at an estimated total cost of less than 5 MSEK.

Based on the above cited costs, the annual cost related to OSA treatment is likely to be in the order of 325 million SEK.

One comparator to HGNS in sleep apnoea treatment regarding costs would be nasal CPAP. The unit price of a CPAP device including a nasal mask system is approximately 4,000 SEK. The application of CPAP in a standard uncomplicated case includes a titration night which may be performed in the patient's home or in the hospital depending on comorbidity and functional status. Evaluation of the recording is made. A follow-up visit is mandatory after 3-6 months. Clinical routines vary quite extensively. The cost for the start-up has been estimated to approximately 8,000 SEK and the following years cost is estimated to approximately 2,000 SEK annually. Individuals with no or poor CPAP compliance generate considerable additional cost due to extra clinical visits, night monitoring, consumption of more consumables, etc. A substantial proportion of non-compliant CPAP patients will be offered an intraoral MRD (unit cost approximately 8,500 SEK).

Expected costs of the new health technology

HGNS will initially be considered in only a very limited group of patients (5-10 per year in Region Västra Götaland). The estimated added cost for the neurostimulator device, clinical diagnostic work-up (four polysomnography studies and staff training) as well as clinical evaluation (propofol study), surgery and postoperative follow-up is estimated to approximately 250,000-270,000 SEK per patient. The life-time cycle of the device has been estimated to approximately 5 years. The functionality is updated by an exchange of the pacing battery.

Total change of cost

HGNS is considerably more expensive (1.25-2.50 MSEK for 5-10 patients) than the conventional treatment options. However, a direct comparison of costs cannot be made as the alternative to HGNS is no treatment or tracheostomy which is rarely practiced. Consequences of untreated OSA (including trauma, cardiovascular events, and metabolic disorder) are currently covered by other sectors of the health care budget.

Possibility to adopt and use the new health technology within the present budget

This is a new technology and it is likely that a separate budget will be required.

Available health economic analyses

A recent health economic analysis performed by investigators associated with the recently published STAR trial suggests that the new technology in patients with moderate-to-severe sleep apnoea was projected to add 1.09 QALYs over the patients´ lifetime. The cost/QALY was calculated to USD 39,471/QALY, which in the UK is considered acceptable (Pietzsch et al., 2104).

10. Unanswered questions

Ongoing research

There are five relevant studies in Clinicaltrials.gov (c.f. Appendix 5)

Important gaps in scientific knowledge

The effects on outcomes 'critical for decision-making', as defined in this HTA analysis, are yet to be determined.
The exact criteria for optimal patient selection (appropriate phenotype) are lacking. The available data suggest that incorrect patient selection provides a major limitation.
Long-term efficacy data and information on device durability beyond 18 months are lacking.
It is unknown if the efficacy-to-risk ratio reported in limited size clinical trials may be maintained if the technique is disseminated to multiple clinical centres.

Interest in the own clinic/research group/organisation to start studies/trials within the research field at issue

No.

10. Unanswered questions

Ongoing research

There are five relevant studies in Clinicaltrials.gov (c.f. Appendix 5)

Important gaps in scientific knowledge

The effects on outcomes 'critical for decision-making', as defined in this HTA analysis, are yet to be determined.
The exact criteria for optimal patient selection (appropriate phenotype) are lacking. The available data suggest that incorrect patient selection provides a major limitation.
Long-term efficacy data and information on device durability beyond 18 months are lacking.
It is unknown if the efficacy-to-risk ratio reported in limited size clinical trials may be maintained if the technique is disseminated to multiple clinical centres.

Interest in the own clinic/research group/organisation to start studies/trials within the research field at issue

No.

Appendix 1, Search strategy, study selection and references

Question(s) at issue:

PICO: *P=Patient I=Intervention C=Comparison O=Outcome*

P Adults with OSA (Obstructive Sleep Apnea) not accepting or tolerating CPAP Treatment

I Electrical hypoglossus nerve stimulation

C No treatment
Other treatment
Electrical hypoglossus nerve stimulator off

O <u>Critical for decision making</u>

Cardiovascular morbidity
Mortality
Traffic accidents

<u>Important but not critical for decision making</u>

ESS (Epworth sleepiness scale)
HRQL (Health related quality of life)
AHI (Apnea-hypopnea index)
ODI (Oxygen desaturation index)
FOSQ (Functional outcomes of sleep questionnaire)
Hypertension
Quality of sleep

<u>Not important for decision making</u>

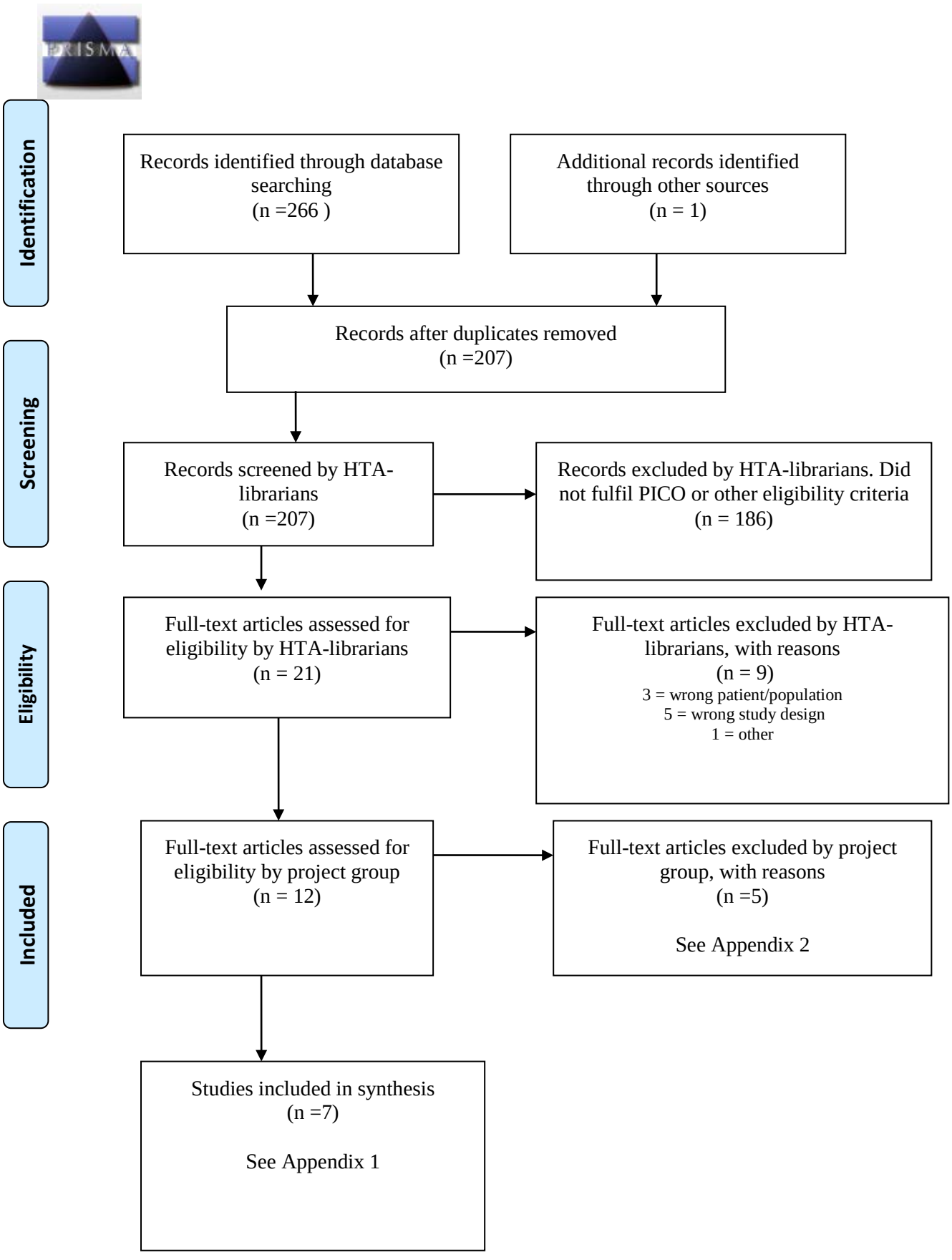
<u>Eligibility criteria</u>

Study design:
All studies except case reports and non-systematic reviews

Language: Danish, English, German, Norwegian, Swedish

Publication date: 1994-

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2014-11-28
No of results: 74

Search	Query	Results
#25	**Search #16 NOT #17** Filters: **Publication date from 1994/01/01; Danish; English; German; Norwegian; Swedish**	**74**
#18	Search #16 NOT #17	87
#17	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1360023
#16	Search #14 NOT #15	95
#15	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3949259
#14	Search #6 AND #12	152
#12	Search #9 OR #10 OR #11	5539
#11	Search upper airway stimulation[tiab]	14
#10	Search Hypogloss*[tiab]	4828
#9	Search "Hypoglossal Nerve"[Mesh]	2870
#6	Search#2 OR #3 OR #4 OR #5	25951
#5	Search OSA[tiab]	7062
#4	Search sleep apnoea[tiab]	4101
#3	Search sleep Apnea[tiab]	19005
#2	Search "Sleep Apnea, Obstructive"[Mesh]	11893

Database: EMBASE (OVID SP)
Date: 2014-11-28
No of results: 165

#	Searches	Results
15	sleep apnea.ti,ab,kw.	28281
16	exp sleep disordered breathing/	15369
17	OSA.ti,ab,kw.	11838
18	sleep apnoea.ti,ab,kw.	6254
19	15 or 16 or 17 or 18	40582
20	hypogloss$.ti,ab,kw.	5164
21	exp hypoglossal nerve/	3026
22	upper airway stimulation.ti,ab,kw.	36

23	20 or 21 or 22	5993
24	19 and 23	284
25	(animal not (animal and human)).sh.	1195420
26	24 not 25	276
27	limit 26 to (danish or english or german or norwegian or swedish)	269
28	limit 27 to yr="1994 -Current"	249
29	limit 28 to (article or conference paper or note or "review")	**165**
30	from 14 keep 1-249	249
31	**limit 30 to (article or conference paper or note or "review")**	**165**

Database: The Cochrane Library
Date: 2014-12-01
No of results: 26
Cochrane reviews 3
Clinical trials 22
Technology assessments 1

ID	Search	Hits
#1	sleep apnea, obstructive or sleep apnoea or sleep apnea or OSA (ti, ab, kw)	3052
#2	hypogloss* or hypoglossal nerve or upper airway stimulation	142
#3	**#1 and #2**	**26**

Database: CRD
Date: 2014-12-01
No of results: 0

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited 2014-11-28
1 reference was found

Reference lists
A comprehensive review of reference lists brought 1 new record

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Reference lists

Included studies:

Eastwood PR, Barnes M, Walsh JH, Maddison KJ, Hee G, Schwartz AR, Smith PL, et al. Treating obstructive sleep apnea with hypoglossal nerve stimulation. Sleep. 2011; 34(11): 1479-1486.

Kezirian EJ, Goding Jr GS, 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.

Mwenge GB, Rombaux P, Dury M, Lengelé B, Rodenstein P. Targeted hypoglossal neurostimulation for obstructive sleep apnoea: a 1-year pilot study. Eur Respir J. 2013; 41(2): 360-367.

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.
Arch Otolaryngol Head Neck Surg. 2001; 127(10): 1216-1223.

Strollo Jr PJ, Soose RJ, Maurer JT, De Vries N, Cornelius J, Froymovich O, et al. Upper-airway stimulation for obstructive sleep apnea. New Eng J Med. 2014; 370(2): 139-149.

Van de Heyning PH, Badr S, 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): 1626-1633.

Woodson BT, Boyd Gillespie M, Soose RJ, Maurer JT, De Vries N, Steward DL, et al. Randomized Controlled Withdrawal Study of Upper Airway Stimulation on OSA: Short- and Long-term Effect. Otolaryngol Head Neck Surg. 2014; 151(5): 880-887.

Excluded studies:

Certal VF, Zaghi S, Riaz M, Vieira AS, Pinheiro CT, Kushida C, et al. Hypoglossal nerve stimulation in the treatment of obstructive sleep apnea: A systematic review and meta-analysis. Laryngoscope. 2014 Nov 12. doi: 10.1002/lary.25032. [Epub ahead of print]

Eisele DW, Smith PL, Alam DS, Schwartz AR. Direct hypoglossal nerve stimulation in obstructive sleep apnea. Arch Otolaryngol Head Neck Surg. 1997; 123(1): 57-61.

Knaack L, Janicki J. Behandlung des obstruktiven Schlafapnoe-Syndrom mittels hypoglossus-nervenstimulation : implantierbare nervenschrittmachersysteme zur behandlung der obstruktiven Schlafapnoe. Atemwegs- und Lungenkrankheiten. 2012;38(11): 473-478.

Safiruddin F, Vanderveken OM, De Vries N, Maurer JT, Lee K, Ni Q, Strohl KP. Effect of upper-airway stimulation for obstructive sleep apnoea on airway dimensions. Eur Respir J.
2015 Jan;45(1):129-38. doi: 10.1183/09031936.00059414. Epub 2014 Sep 3.

Guilleminault C, Powell N, Bowman B, Stoohs R. The effect of electrical stimulation on obstructive sleep apnea syndrome. Chest. 1995;107(1):67-73.

Other references:

Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. Thorax. 2013 Sep;68(9):846-53.

Carlson JT, Rångemark C, Hedner JA. Attenuated endothelium-dependent vascular relaxation in patients with sleep apnoea. J Hypertens. 1996 May;14(5):577-84.

Checklists from SBU regarding randomized controlled trials. [Internet]. [cited 2015 Feb 26] Available from: http://www.sahlgrenska.se/upload/SU/HTA-centrum/Hj%c3%a4lpmedel%20under%20projektet/B02_Granskningsmall%20f%c3%b6r%20%20randomiserad%20kontrollerad%20pr%c3%b6vning%20RCT%202014-10-29.doc

GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490-4.

GRADE Working Group. List of GRADE working group publications and grants [Internet]. [Place unknown]: GRADE Working Group, c2005-2009 [cited 2012 Mar 8]. Available from: http://www.gradeworkinggroup.org/publications/index.htm

Grote L, Ploch T, Heitmann J, Knaack L, Penzel T, Peter JH. Sleep-related breathing disorder is an independent risk factor for systemic hypertension. Am J Respir Crit Care Med. 1999 Dec;160(6):1875-82.

Grote L, Zou D, Kraiczi H, Hedner J. Finger plethysmography--a method for monitoring finger blood flow during sleep disordered breathing. Respir Physiol Neurobiol. 2003 Jul 16;136(2-3):141-52.

Guo B, Moga C, Schopflocher D, Harstall C. Validation of a quality assessment checklist for case series studies. In: Better Knowledge for Better Health | Un meilleur savoir pour une meilleure santé. Abstracts of the 21st Cochrane Colloquium; 2013 19-23 Sep; Québec City, Canada. John Wiley & Sons; 2013.

Hedner J, Ejnell H, Sellgren J, Hedner T, Wallin G. Is high and fluctuating muscle nerve sympathetic activity in the sleep apnoea syndrome of pathogenetic importance for the development of hypertension? J Hypertens Suppl. 1988 Dec;6(4):S529-31.

Karimi M, Hedner J, Häbel H, Nerman O, Grote L. A Sleep Apnea-Related Risk of Motor Vehicle Accidents is Reduced by Continuous Positive Airway Pressure: Swedish Traffic Accident Registry Data. Sleep. 2015 Mar 1;38(3):341-9.

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

Olaithe M, Bucks RS. Executive dysfunction in OSA before and after treatment: a meta-analysis. Sleep. 2013 Sep 1;36(9):1297-305.

Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. Eur Respir J. 2006 Sep;28(3):596-602. Epub 2006 Apr 26.

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

Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med. 2010 Jul 15;182(2):269-77.
Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993 Apr 29;328(17):1230-5.

Sánchez-de-la-Torre M, Nadal N, Cortijo A, Masa JF, Duran-Cantolla J, Valls J, Serra S, Sánchez-de-la-Torre A, Gracia M, Ferrer F, Lorente I, Urgeles MC, Alonso T, Fuentes A, Armengol F, Lumbierres M, Vázquez-Polo FJ, Barbé F; Respiratory Medicine Research Group. Role of primary care in the follow-up of patients with obstructive sleep apnoea undergoing CPAP treatment: a randomised controlled trial. Thorax. 2015 Apr;70(4):346-52.

Vanderveken OM, Braem MJ, Dieltjens M, De Backer WA, Van de Heyning PH. Objective measurement of the therapeutic effectiveness of continuous positive airway pressure versus oral appliance therapy for the treatment of obstructive sleep apnea. Am J Respir Crit Care Med. 2013 Nov 1;188(9):1162.

Zou D, Grote L, Radlinski J, Eder DN, Lindblad U, Hedner J. Nocturnal pulse wave attenuation is associated with office blood pressure in a population based cohort. Sleep Med. 2009 Sep;10(8):836-43.

Appendix 2 – Included studies – design and patient characteristics.

Author, year,	Country	Study Design	No of participants	Patient characteristics	Intervention	Outcomes
Eastwood, 2011	Australia	Case-series	21	Age: 53.6 SD ± 9.2 Male (%): 67 BMI: 32.7 SD ± 3.6	HGNS Apnex	AHI ODI ESS FOSQ HRQL (SAQLI, BDI) Quality of sleep (PSQI, PSG data)
Kezirian, 2014	Australia, USA	Case series	32, one device explanted before use	Age: 52.4 SD ± 9.4 Male (%): 65 BMI: 32.4 SD ± 3.6	HGNS Apnex	AHI ODI ESS FOSQ HRQL (SAQLI, BDI) Quality of sleep (PSQI, PSG data)
Mwenge, 2013	Belgium	Case series	14, 13 devices successfully implanted	Age: 50.3 Male (%): 93 BMI: 30.5	HGNS, ImThera Aura 6000	AHI ODI ESS FSS Quality of sleep (PSG data)
Schwarz, 2001	USA, Germany, Sweden, Belgium, Netherlands	Case series	8	Age: 49.9 Male (%): 100 BMI: 28.4 SD ± 4.5	HGNS, Inspire I, Medtronic	AHI ODI Quality of sleep (PSG data)
Strollo, 2014	USA, Germany, Belgium, Netherlands, France	RCT / case series	46/126	N=126 Age: 54.5 SD ± 10.2 Male (%): 83 BMI: 28.4 SD ± 2.6	HGNS, Inspire Medical System	AHI ODI Predefined responder rate ESS FOSQ

Appendix 2 – Included studies – design and patient characteristics.

Author, year,	Country	Study Design	No of participants	Patient characteristics	Intervention	Outcomes
Van de Heyning, 2012	USA, Germany, Belgium, Israel	Case series, two separate subpopulations	22/9; 2/1 devices explanted	N=20/8 Age: 55.7 /53.6 Male (%): 100/88 BMI: 29.8/28.9	HGNS, Inspire II	AHI ODI ESS FOSQ Quality of sleep (PSG data)
Woodson, 2014	USA, Germany, Netherlands	RCT	46 (46 patients followed until 18 months from Strollo, 2014)	Age: 54.9 Male (%): 89 BMI: 27.9	HGNS, Inspire Medical System	AHI ODI ESS FOSQ Quality of sleep (PSG data)

AHI=Apnea Hypopnea Index

ODI=Oxygen Desaturation Index

ESS= Epworth Sleepiness Scale

FOSQ= Functional Outcomes of Sleep Questionnaire

HGNS= Hypoglossal nerve stimulation

Project: HGNS for OSA
Appendix 3. Excluded articles

Study author, publication, year	Reason for exclusion
Certal, 2014	Metaanalysis data, no new patient data
Eisele, 1997	Wrong outcomes
Knaack, 2012	Nonsystematic review, no new patient data
Safiruddin, 2014	Subgroup analysis of STAR Trial data (Strollo et al 2014)
Guilleminault, 1995	Wrong intervention: direct muscle stimulation; Wrong P: not the intended patient population; Wrong outcome measures

Table 4-1. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Apnea-hypopnea index (AHI), events per hour of sleep

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Strollo, 2014	USA, Germany, Belgium, Netherlands, France	RCT (Randomized withdrawal design)	n=46 I=23 C=23	2	AHI Baseline (12 months): 7.2 events/h After 1 week: 8.9 events/h Δ = 1.7 events/h	AHI Baseline (12 months): 7.6 events/h After 1 week: 25.8 events/ Δ = 18.2 events/h p<0.001, between groups	Device: Inspire® After 12 months, the therapy maintenance group (I) continued nightly use of the device. In the therapy-withdrawal group (C) the device was turned off for at least 5 days prior to polysomnography (after 1 week).	+	?/+	+
		Case series	n=126		AHI Baseline: 32.0 (11.8) 12 months: 15.3 (16.1) Δ = -16.4 (16.7) events/h p<0.001, within group	NA				
Eastwood, 2011	Australia	Case series	n=21	2	AHI Baseline: 43.1 (17.5) 3 months: 19.0 (10.7) p<0.001 6 months: 19.5 (16.7) p<0.001	NA	Device: Apnex® Wide inclusion criteria with AHI 20-100 events/h	?/+	+	+
Kezirian, 2014	Australia, USA	Case series	n=32	1	Baseline: 45.4 (17.5) 6 months: 20.8 (17.6) p<0.001 12 months: 25.3 (20.6) p<0.001	NA	Device: Apnex® 21 patients from Eastwood, 2011, and 11 patients from another centre followed up for 12 months.	?	+	+

Table 4-1. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Apnea-hypopnea index (AHI), events per hour of sleep

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Mwenge, 2013	Belgium	Case series	n=14	1	AHI Baseline: 45.2 (17.8) 3 months: 21.7 (19.9) p<0.001 12 months: 21.0 (16.5) p<0.001	NA	Device: ImThera, Aura 6000^{TM} No objective data on device usage.	?	?	?
Schwarz, 2001	USA, Germany, Sweden, Belgium, Netherlands	Case series	8	0	AHI NREM sleep Baseline: 52.0 (20.4) 6 months: 22.6 (12.1) p<0.001 AHI REM sleep Baseline: 48.2 (30.5) 6 months: 16.6 (17.1) p<0.001	NA	Device: HGNS, Inspire I, Medtronic Small, early pilot study. After end of the study: 5 devices with loss of adequate function. No objective data on device usage.	?	?	?

Table 4-1. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Apnea-hypopnea index (AHI), events per hour of sleep

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Van de Heyning, 2012	USA, Germany, Belgium, Israel	Case series, two separate sub-populations	22/9;	2/1 devices explanted	AHI population part I, n=20 Baseline: 43.6 (18.4) 6 months: Separate analysis for responders (n=6) and Non-responders (n=14) ns. difference for the total cohort AHI population part II, n=8 Baseline: 38.9 (9.8) 6 months:10.0 (11.0) P<0.01	NA	Device: Inspire Medical Systems. 2 study populations. First population showed 14 non-responders and 6 responders according to predefined criteria. Predictors for response were identified: BMI≤32 kgm^{-2}, AHI≤50 events/hour Predictors were used as inclusion criteria in the second study population.	?	?	?/-

Table 4-1. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Apnea-hypopnea index (AHI), events per hour of sleep

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Woodson, 2014	USA, Germany, Netherlands	Case series	46	0	AHI for "device on" group Baseline: 31.3 (12.3) 18 months device on: 9.6 (11.3) p<0.05 AHI for "device off" group Baseline: 30.1 (11.4) 18 months device on: 10.7 (7.3) P<0.05	NA	Device: Inspire Medical Systems. Data from RCT Strollo, 2014 followed up at 18 months.	+	?/+	+

NA= Not applicable

Table 4-2. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: ODI (Oxygen desaturation index), events per hour of sleep

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Strollo, 2014	USA, Germany, Belgium, Netherlands, France	RCT (Randomized withdrawal design)	n=46 I=23 C=23	2	ODI Baseline (12 months): 6.3 After 1 week: 8.0 Δ = 1.7	ODI Baseline (12 months): 6.0 After 1 week: 23.0 Δ = 17.0 p<0.001, between groups	Device: Inspire® After 12 months, the therapy maintenance group (I) continued nightly use of the device. In the therapy-withdrawal group (C) the device was turned off for at least 5 days prior to polysomnography (after 1 week).	+	?/+	+
		Case series	n=126		ODI Baseline: 28.9 (12.0) 12 months: 13.9 (15.7) Δ = -14.6 (15.8) p<0.001 within group	NA				
Eastwood, 2011	Australia	Case series	n=21	2	ODI Baseline: 16.8 (14.4) 3 months: 8.0 (7.8) p<0.001 6 months: 9.1 (16.7) p<0.001	NA	Device: Apnex® Wide inclusion criteria with AHI 20-100 events/h	?/+	+	+

Table 4-2. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: ODI (Oxygen desaturation index), events per hour of sleep

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Kezirian, 2014	Australia, USA	Case series	n=32	1	ODI Baseline: 20.9 (17.3) 6 months: 10.7 (17.1) p<0.001 12 months: 15.7 (19.6) p<0.001	NA	Device: Apnex® 21 patients from Eastwood, 2011, and 11 patients from another centre followed up for 12 months.	?	+	+
Mwenge, 2013	Belgium	Case series	n=14	1	ODI Baseline: 29.2 (19.6) 3 months: 14.2 (16.7) p<0.001 12 months: 15.3 (16.2) p=0.001	NA	Device: ImThera, Aura 6000™ No objective data on device usage.	?	?	?

Table 4-2. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: ODI (Oxygen desaturation index), events per hour of sleep

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Van de Heyning, 2012	USA, Germany, Belgium, Israel	Case series, two separate sub-populations	22/9;	2/1 devices explanted	ODI population part I, n=20 Baseline: 30.1 (24.0) 6 months: Separate analysis for responders (n=6) and Non-responders (n=14) Difference in the whole series not reported ODI population part II, n=8 Baseline: 32.1 (15.1) 6 months: 9.5 (10.2) p<0.01	NA	Device: Inspire Medical Systems. 2 study populations. First population showed 14 non-responders and 6 responders according to predefined criteria. Predictors for response were identified: BMI≤32 kgm^{-2}, AHI≤50 events/hour Predictors were used as inclusion criteria in the second study population.	?	?	?/-

Table 4-2. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: ODI (Oxygen desaturation index), events per hour of sleep

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Woodson, 2014	USA, Germany, Netherlands	Case series	46	0	ODI for “device on” group Baseline: 26.7 (13.0) 18 months device on: 8.6 (11.0) p<0.05 ODI for “device off” group Baseline: 26.8 (10.2) 18 months device on: 9.1 (6.1) p<0.05	NA	Device: Inspire Medical Systems. Data from RCT Strollo, 2014 followed up at 18 months.	+	?/+	+

NA= Not applicable
ODI= Oxygen Desaturation Index (number of desaturations per hour of sleep)

Table 4-3. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: ESS (Epworth sleepiness scale)

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Strollo, 2014	USA, Germany, Belgium, Netherlands, France	Case series	n=126	2	ESS Baseline: 11.6 (5.0) 12 months: 7.0 (4.2) Δ = -4.7 (5.0) p<0.001	NA	Device: Inspire® After 12 months, the therapy maintenance group (I) continued nightly use of the device. In the therapy-withdrawal group (C) the device was turned off for at least 5 days prior to polysomnography (after 1 week).	+	?/+	+
Eastwood, 2011	Australia	Case series	n=21	2	ESS Baseline: 12.1 (4.7) 3 months: 7.9 (4.0) p<0.001 6 months: 8.1 (4.4) p<0.001	NA	Device: Apnex® Wide inclusion criteria with AHI 20-100 events/h	?/+	+	+
Kezirian, 2014	Australia, USA	Case series	n=32	1	ESS Baseline: 12.1 (4.6) 6 months: 8.3 (3.6) p<0.001 12 months: 7.9 (3.8) p<0.001	NA	Device: Apnex® 21 patients from Eastwood, 2011, and 11 patients from another centre followed up for 12 months.	?	+	+
Mwenge, 2013	Belgium	Case series	n=14	1	ESS Baseline: 10.8 (6.2) 3 months: 6.7 (5.4) p=0.023 12 months: 7.9 (4.2) ns.	NA	Device: ImThera, Aura 6000™ No objective data on device usage.	?	?	?

Table 4-3. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: ESS (Epworth sleepiness scale)

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Van de Heyning, 2012	USA, Germany, Belgium, Israel	Case series, two separate subpopulations	22/9;	2/1 devices explanted	ESS No significant difference. Data not shown.	NA	Device: Inspire Medical Systems. 2 study populations. First population showed 14 non-responders and 6 responders according to predefined criteria. Predictors for response were identified: BMI≤32 kgm^{-2}, AHI≤50 events/hour Predictors were used as inclusion criteria in the second study population.	?	?	?/-
Woodson, 2014	USA, Germany, Netherlands	Case series	46	0	ESS for "device on" group Baseline: 11.2 (5.3) 18 months device on: 6.0 (3.7) p<0.05 ESS for "device off" group Baseline: 11.3 (5.0) 18 months device on: 8.0 (4.4) p<0.05	NA	Device: Inspire Medical Systems. Data from RCT Strollo, 2014 followed up at 18 months.	+	?/+	+

NA=Not applicable
ESS= Epworth Sleepiness Scale range from 0-24, where a higher score indicates increased risk to fall asleep during daily activities. Minimally important difference not defined. Clinical threshold for hypersomnia is approx. ≥11.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Strollo, 2014	USA, Germany, Belgium, Netherlands, France	Case-series	n=126	2	FOSQ Baseline: 14.3 (3.2) 12 months: 17.3 (2.9) Δ = 2.9 (3.1) p<0.001	NA	Device: Inspire® After 12 months, the therapy maintenance group (I) continued nightly use of the device. In the therapy-withdrawal group (C) the device was turned off for at least 5 days prior to polysomnography (after 1 week).	+	?/+	+
Eastwood, 2011	Australia	Case-series	n=21	2	FOSQ Baseline: 14.4 (2.0) 3 months: 17.0 (2.0) p<0.001 6 months: 16.7 (2.2) p<0.001	NA	Device: Apnex® Wide inclusion criteria with AHI 20-100 events/h	?/+	+	+
Kezirian, 2014	Australia, USA	Case-series	n=32	1	FOSQ Baseline: 14.2 (2.0) 6 months: 16.8 (2.4) p<0.001 12 months: 17.0 (2.4) p<0.001	NA	Device: Apnex® 21 patients from Eastwood, 2011, and 11 patients from another centre followed up for 12 months.	?	+	+

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off Mean (SD) if not otherwise stated				
Van de Heyning, 2012	USA, Germany, Belgium, Israel	Case series, two separate subpopulations	22/9;	2/1 devices explanted	FOSQ No significant difference, no specific values shown.	NA	Device: Inspire Medical Systems. 2 study populations. First population showed 14 non-responders and 6 responders according to predefined criteria. Predictors for response were identified: BMI≤32 kgm^{-2}, AHI≤50 events/hour Predictors were used as inclusion criteria in the second study population.	?	?	?/-
Woodson, 2014	USA, Germany, Netherlands	Case series	46	0	FOSQ for "device on" group Baseline: 15.1 (3.1) 18 months device on: 18.0 (2.9) p<0.05 FOSQ for "device off" group Baseline: 13.9 (2.6) 18 months device on: 17.1 (2.9) p<0.05	NA	Device: Inspire Medical Systems. Data from RCT Strollo, 2014 followed up at 18 months.	+	?/+	+

NA=Not applicable
FOSQ= 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).

Table 4-5. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Sleep Quality

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off				
Strollo, 2014	USA, Germany, Belgium, Netherlands, France	Case series	n=126	n=2	<u>Total sleep (min)</u> Baseline: 364.8 (68.0) 12 mo: 333.7 (69.3), p <0.0001 <u>N1 sleep (min)</u> Baseline 42.0 (21.0) 12 mo: 31.1 (15.9), p <0.0001 <u>N2 sleep (min)</u> Baseline: 234.5 (56.0) 12 mo: 214.3 (60.2), p= 0.0002 <u>N3 sleep (min)</u> Baseline: 31.0 (27.6) 12 mo: 36.0 (31.5) , p= 0.03 <u>REM sleep (min)</u> Baseline: 57.3 (27.4) 12 mo: 52.2 (33.8), p= 0.08 <u>Arousal index</u> Baseline: 29 12 mo: 15, p<0.001	NA	Device: Inspire® After 12 months, the therapy maintenance group (I) continued nightly use of the device. In the therapy-withdrawal group (C) the device was turned off for at least 5 days prior to polysomnography (after 1 week).	+	?/+	+

Table 4-5. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Sleep Quality

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off				
Eastwood, 2011	Australia	Case series	n=21	n=2	<u>Total sleep (min)</u> Baseline: 340 (64) 3 mo: 363 (66), n.s. 6 mo: 350 (58), n.s. <u>N1 %</u> Baseline: 27 (10.0) 3 mo: 18 (8), p =0.003 6 mo: 21 (12), p=0.003 <u>REM %</u> Baseline: 14 (6) 3 mo: 18 (4), p=0.006 6 mo: 17 (6), p=0.02 <u>Arousal index</u> Baseline: 44 3 mo: 23, p=0.015 6 mo: 24, p<0.001 <u>Other sleep stages</u> Without sign. change	NA	Device: Apnex® Wide inclusion criteria with AHI 20-100 events/h	?/+	+	+

Table 4-5. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Sleep Quality

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off				
Kezirian, 2014	Australia, USA	Case series	n=32	n=1	<u>Sleep efficiency %:</u> Baseline: 77.2 (13) 6 mo: 82.8 (11), p<0.05 12 mo: 82.6 (10), p<0.05 <u>N1 %</u> Baseline 29 (11) 6 mo: 21 (10), p <0.001 12 mo:22 (10), p<0.001 <u>REM %</u> Baseline: 13 (7) 6 mo: 16 (6), p<0.05 12 mo: 16 (5), p<0.05. <u>Arousal index (awakenings/h)</u> Baseline: 44 6 mo: 24, p<0.001 12 mo: 28, p<0.001 <u>Other sleep stages</u> without sign. change	NA	Device: Apnex® 21 patients from Eastwood, 2011, and 11 patients from another centre followed up for 12 months.	?	+	+
Mwenge, 2013	Belgium	Case series	n=14	n=1	No significant changes in sleep efficiency, N1, N2, N3 and REM sleep stages (%). <u>Arousal index (awakenings/h)</u> Baseline: 37 3 mo: 25, p<0.001 12 mo: 25, p=0.001	NA	Device: ImThera, Aura 6000™ No objective data on device usage.	?	?	?

Table 4-5. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Sleep Quality

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention HGNS on Mean (SD) if not otherwise stated	Control HGNS off				
Schwarz, 2001	USA, Germany, Sweden, Belgium, Netherlands	Case series	n=8	n=0	No significant changes in total sleep time, sleep efficiency, N1, N2, N3 and REM sleep stages (%). Means for N3 and REM increase but the changes are not significant.	NA	Device: HGNS, Inspire I, Medtronic Small, early pilot study. After end of the study: 5 devices with loss of adequate function. No objective data on device usage.	?	?	?
Van de Heyning, 2012	USA, Germany, Belgium, Israel	Case series two separate subpopulations	n=22/9	n=2/1 devices explanted	Sleep data are shown for responders and non-responders in the first study population. In the second study population (n=8) no significant changes were observed for total sleep time, sleep efficiency, sleep stage % for N1, N2, N3, and REM sleep	NA	Device: Inspire Medical Systems. 2 study populations. First population showed 14 non responders and 6 responders according to predefined criteria. Predictors for response were identified: BMI≤32 kgm^{-2}, AHI≤50 events/hour Predictors were used as inclusion criteria in the second study population.	?	?	?/-
Woodson, 2014	USA, Germany, Netherlands	Case series	n=46	n=0	"Device on" group: <u>Arousal index (awakenings/h)</u> Baseline: 31 18 mo: 15, p<0.05. "Device off" group: <u>Arousal index (awakenings/h)</u> Baseline: 26 18 mo: 17, p<0.05. No significant changes were observed for total sleep time, sleep efficiency, sleep stage % for N1, N2, N3, and REM sleep-	NA	Device: Inspire Medical Systems. Data from RCT Strollo, 2014 followed up at 18 months.	+	?/+	+

NA=Not Applicable, Mo= months
Sleep stages:
N1= Non REM sleep stage 1 ("light sleep") N2= Non REM sleep stage 2 ("light sleep") N3= Non REM sleep stage 3 ("deep sleep") REM= Rapid Eye Movement sleep

Table 4-6. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Complications

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations*	Precision*
					Intervention HGNS on	Control HGNS off				
Strollo, 2014	USA, Germany, Belgium, Netherlands, France	RCT (withdrawal design)	n=46 I=23 C=23	n=0	RCT – no adverse events reported	Not reported	Device: Inspire® After 12 months, the therapy maintenance group (I) continued nightly use of the device. In the therapy-withdrawal group (C) the device was turned off for at least 5 days prior to polysomnography (after 1 week).	+	?/+	+
		Case series	n=126		Case series: 2 SAE related to HGNS device: Discomfort requiring repositioning of the electrode 33 SAE not related to HGNS device: 2 deaths (cardiac event, homicide),: coronary artery disease, arrhythmias, and chest pain (n = 8), accidents or injuries (n = 11), and other surgeries (n=12). Device related AE: 190, procedure related AE: 169 including discomfort with neurostimulation and tongue sourness. Most events resolved over time.	NA				
Eastwood, 2011	Australia	Case series	n=21	n=2	Surgical procedure: 8/21 cuff repositioning, 2 devices explanted, 1 cuff dislodgement. AE related to implantation and to HGNS therapy 71 and 67%: discomfort, tongue abrasions.	NA	Device: Apnex® Wide inclusion criteria with AHI 20-100 events/h	?/+	+	+
Kezirian, 2014	Australia, USA	Case-series	n=32	n=1	No death; 3/31 (10%) SAE to therapy (not further specified), 4 devices explanted, 2 lead cuff dislodgement (successfully re-operated), psychological disturbance (n=1), minor AE reported in 22/31 (71%) related to the surgical procedure, 3/31 (10%) minor AE related to start of nerve stimulation (tongue abrasions, self-limited)	NA	Device: Apnex® 21 patients from Eastwood, 2011, and 11 patients from another centre followed up for 12 months.	?	+	+
Mwenge, 2013	Belgium	Case series	n=14	n=1	No death, no device explanted. 5 SAE (1 defective connector, 4 broken lead, and/or defective stimulator) , 54 AE ((ipsilateral hemi tongue paresis, fully recovered (2), dysphagia, recovered (1), technical problems (n=45)); 100% technical problems (transient treatment interruptions due to problems with external device). 1 patient not implanted due to technical SAE, all 13 remaining patients continued therapy despite AE/SAE.	NA	Device: ImThera, Aura 6000™ No objective data on device usage.	?	?	?

Table 4-6. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea
Outcome variable: Complications

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result		Comments	Directness*	Study limitations*	Precision*
					Intervention HGNS on	Control HGNS off				
Schwarz, 2001	USA, Germany, Sweden, Belgium, Netherlands	Case series	n=8	n=0	No death, 3/8 pts with technical problem (device malfunction (1), respiratory synchronisation (2)). At long term follow-up 2/8 pts suffered from lead malfunction (after study termination).	NA	Device: HGNS, Inspire I, Medtronic Small, early pilot study. After end of the study: 5 devices with loss of adequate function. No objective data on device usage.	?	?	?
Van de Heyning, 2012	USA, Germany, Belgium, Israel	Case series, two separate subpopulations	n=22/9;	n=2/1 devices explanted	No death, 2 SAE related to transient infections. 15 AE related to stimulation (e.g. tongue stiffness and sore throat).	NA	Device: Inspire Medical Systems. 2 study populations. First population showed 14 non responders and 6 responders according to predefined criteria. Predictors for response were identified: BMI≤32 kgm^{-2}, AHI≤50 events/hour Predictors were used as inclusion criteria in the second study population.	?	?	?/-
Woodson, 2014	USA, Germany, Netherlands	Case series	n=46	n=0	No deaths, no SAE or AE reported.	NA	Device: Inspire Medical Systems. Data from RCT Strollo, 2014 followed up at 18 months.	+	?/+	+

AE = Adverse event, AHI=Apnea Hypopnea Index, NA= Not applicable, SAE = Severe adverse event

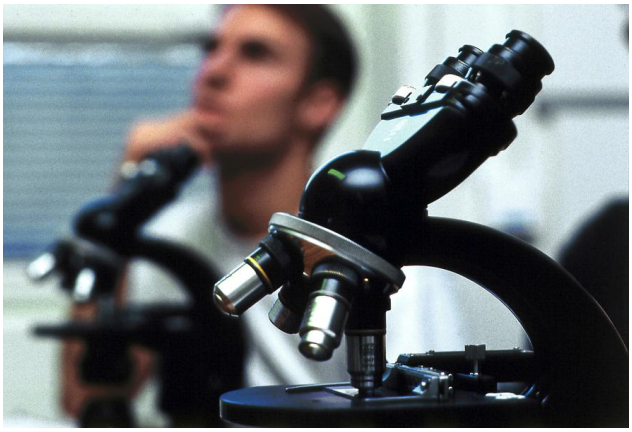
Appendix 5. Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea.
Ongoing Research (Clinical Trials.gov)

Study	Clinical Trial-Id	Country	Study Design	Estimated No. of participants	Start	Estimated Completion (primary data)	Primary Outcomes	HGNS	Current status
Apnex Clinical Study of the Hypoglossal Nerve Stimulation (HGNS) System to Treat Obstructive Sleep Apnea,	NCT 01446601	USA, Australia	6 month RCT: The control arm is implanted with the HGNS system and therapy is turned on at 7 months post-implant. 12 month case series	132	Aug 2011	Oct 2017 (Oct 2013)	Reduction in OSA severity: 6 months compared to control, and 12 months compared to baseline. Safety analysis at 12 months	Apnex	Recruiting
US Clinical Study of the Apnex Medical Hypoglossal Nerve Stimulation (HGNS) System to Treat Obstructive Sleep Apnea	NCT 01211444	USA	Case series	20	Jul 2010	Sep 2016 (Sep 2013)	Mean change in AHI at 6 months compared to baseline, mean change in FOSQ compared to baseline, SAE frequency	Apnex	Ongoing, but no longer recruiting.
Targeted Hypoglossal Neurostimulation Study #3 (THN3)	NCT 02263859	USA, Belgium, Germany	4 month RCT: control group implanted with HGNS will receive treatment as usual, (i.e. any non-surgical OSA treatment including PAP, oral appliances and positional devices) until 14 days (washout) prior to the month 4 visit. HGNS then turned on. 12 month case series	141	Nov 2014	May 2021 (May 2016)	AHI and ODI change at 4 months compared to control, AHI and ODI responder rate, safety analysis at 12 months	ImThera Medical aura6000	Not yet recruiting
Inspire® Upper Airway Stimulation (UAS) System German Post-Market Study	NCT 02293746	Germany	Case series	60	Jun 2014	Apr 2016	No. reported SAEs/procedure and device related AEs at 12 months (change in AHI,ODI, ESS, FOSQ secondary)	Inspire® Upper Airway Stimulation (UAS) System	Recruiting
Safety and Performance Study of the Nyxoah SAT System for Treating OSA	NCT 02312479	Belgium, Germany	Case series	15	Dec 2014	Aug 2015	Incidence of SAE, Mean change in AHI after 6 months	Nyxoah SAT system (muscle + indirect HGNS)	Recruiting

AHI=Apnea Hypopnea Index, ESS= Epworth Sleepiness Scale, FOSQ= Functional Outcomes of Sleep Questionnaire, ODI=Oxygen Desaturation Index, SAE = Serious Adverse Event

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

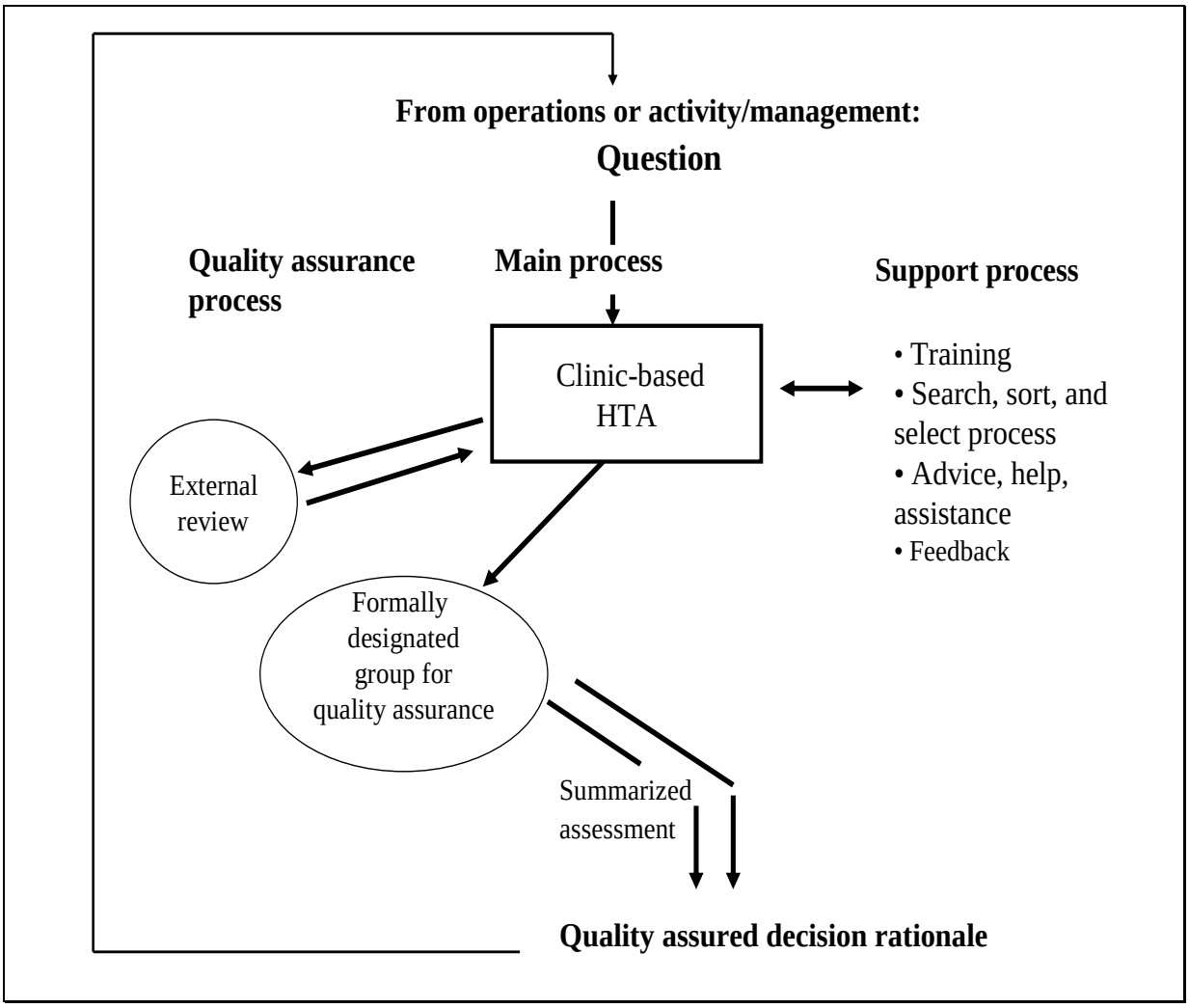
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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