Successful upper airway stimulation therapy in an adult Down syndrome patient with severe obstructive sleep apnea

Upper airway stimulation therapy in Down syndrome patients with obstructive sleep apnea: a review of the literature and an adult case.

Eli Van de Perck[1*], Jolien Beyers[1,2*], Marijke Dieltjens[1,2], Sara Op de Beeck[1,2], Johan Verbraecken[3,4], Paul Van de Heyning[1,2], An Boudewyns[1,2], Olivier M. Vanderveken[1,2,3]

[*]Equal contribution, [1] Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium, [2] Department of Otorhinolaryngology, Head and Neck Surgery, Antwerp University Hospital, Edegem, Belgium, [3] Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital, Edegem, Belgium, [4] Department of Pulmonology, Antwerp University Hospital, Edegem, Antwerp, Belgium

Corresponding author: ~~Eli Van de Perck, University of Antwerp, Faculty of Medicine and Health Sciences, Universiteitsplein 1, 2610 Wilrijk, Belgium. E-mail:~~

Prof. Dr. Olivier M. VANDERVEKEN

Department of ENT, Head and Neck Surgery

Faculty of Medicine and Health Sciences,

University of Antwerp,

Antwerp University Hospital

Wilrijkstraat 10

2650 Edegem

BELGIUM

~~eli.vandeperck@student.uantwerpen.be~~olivier.vanderveken@uza.be

Conflict of interest: Olivier Vanderveken has the following potential conflicts of interest ~~related to the topic of the manuscript~~: research support and lecture fees from Inspire Medical Systems, research grant from and consultancy for Philips Respironics, research grant and lecture fees from Somnomed, consultancy for N~~a~~yxoah, consultancy for Galvani, research support from ReVent, research support from Nightbalance. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Met opmaak: Afstand Na: 0 pt

Met opmaak: Uitvullen, Afstand Na: 0 pt

Met opmaak: Uitvullen, Afstand Na: 0 pt, Regelafstand: Dubbel

Met opmaak: Engels (Verenigde Staten)

Met opmaak: Nederlands (België)

Met opmaak: Nederlands (België)

Funding: Olivier Vanderveken holds a Senior Clinical Investigator Fellowship from the Research Foundation—Flanders (FWO)—2016-2021. Marijke Dieltjens holds a Postdoctoral fellowship at Research Foundation—Flanders (FWO)—12H4516N.

Abstract

Purpose: The aim of this study was to report on the succesfull application of upper airway stimulation (UAS) therapy in an adult down syndrome (DS) patient with severe obstructive sleep apnea (OSA) and CPAP intolerance and to perform a literature search of the current evidence regarding respiration-synchronized electrostimulation of the hypoglossal nerve ~~hypoglossal nerve stimulation~~using UAS in patients with ~~down syndrome (~~DS~~),~~ ~~and in addition, to report the application of this therapy in an adult DS patient with severe OSA and unsuccessful CPAP treatment.~~

Methods: A review of relevant articles retrieved from online databases (PubMed, Web of Science, Cochrane Library) was performed. The 23 years old male OSA patient we report on (apnea/hypopnea index (AHI) 61.5 events/hour and oxygen desaturation index (ODI) 39.7 events/hour at baseline) fulfilled the formal inclusion criteria for ~~upper airway stimulation~~UAS therapy: AHI between 15 and 65 events/hour, body mass index (BMI) < 32 kg/m² and no complete concentric collapse at the level of the velopharynx during drug-induced sleep endoscopy.

Results: Based on the available literature, ~~hypoglossal nerve stimulation~~UAS therapy has a good effect on OSA severity in the paediatric DS population. Implantation of the hypoglossal nerve stimulator in our adult patient with DS resulted in a substantial subjective as well as objective improvement of OSA (63% decrease in AHI and 77% decrease in ODI), translating into an overall satisfactory outcome.

Conclusion: Research on the effectiveness of ~~hypoglossal nerve stimulation~~UAS therapy on the long-term in a large dataset of patients with DS is needed. However, based on the available literature and our presented case, it can be concluded that respiration-synchronized electrostimulation of the hypoglossal nerve hypoglossal nerve stimulation using UAS therapy ~~hypoglossal nerve stimulation~~ has a potential value in well-selected OSA patients with DS that are noncompliant to CPAP ~~-~~therapy.

Key words: sleep-disordered breathing, hypoglossal nerve stimulation, treatment, surgery.

Introduction

Down syndrome (DS) is the most common genetic disorder, with an incidence of 1 in 691 births [1]. Patients with DS are predisposed to a number of health problems affecting their development and quality of life. Among them, obstructive sleep apnea (OSA) is very common, occurring in up to 66% of the children, and in the vast majority of the adults [2, 3]. These patients suffer usually from a more severe OSA with significant hypoxemia as compared with individuals without DS [3]. Consequently, patients with DS are more susceptible to cognitive difficulties and neurodegeneration [4]. Lal et al. have described the impact of OSA on patients with DS in a comprehensive literature review [5]. Early recognition and adequate treatment of OSA may improve their quality of life substantially. Behavioural modifications such as weight loss by exercise and dietary programs or avoidance of noxious fumes might help decreasing the OSA severity. [5]. When these simple measures are not applicable or not sufficient, other or additive treatment options are necessary. Continuous positive airway pressure (CPAP) is the golden standard treatment for adults, with or without DS, with moderate to severe OSA [6, 5]. Nevertheless treatment is of utmost importance, except for CPAP and one study on ~~OA~~oral appliance therapy in only 2 patients, no other treatment options have been investigated in adults with DS and OSA [3, 7]. Electrical neurostimulation of the hypoglossal nerve – using the Inspire II system (*Inspire Medical Systems Inc., Maple Grove, MN, USA*) – referred to as upper airway stimulation (UAS) therapy, has been recently approved for commercial use in selected patients with OSA [8-10]. In this paper, an overview of the literature on respiration-synchronized electrostimulation of the hypoglossal nerve hypoglossal nerve stimulation using UAS therapy ~~hypoglossal nerve stimulation~~ in patients with DS is given. In addition, a case report is presented that was, to the best of our knowledge, the first hypoglossal nerve stimulator ever implanted in an adult patient with DS and OSA.

Review of the literature

Obstructive sleep apnea (OSA) has a great impact on the health of patients with Down syndrome (DS) and despite the significant amount of studies that have been published on upper airway stimulation (UAS) in the general population, only few studies have evaluated the effect of this treatment option in DS patients with OSA. Moreover, all the studies published up to this date were ~~carried out in~~reporting on the paediatric and adolescent population with DS. So far, no studies were published on the application of UAS in adult patients with DS. Keywords used for the literature search were "Down syndrome and hypoglossal nerve stimulation" and "Down syndrome and upper airway stimulation". The search strategy is explained in detail in figure 1. Three databases were searched: Pubmed, Web of Science and Cochrane Library. References were screened on title and abstract at first. A next selection was made based on the full text of the manuscripts. One case report [11] was excluded at this stage because a more recent article implemented this case in a series of 6 patients [12]. References of all articles were screened but no additional relevant articles could be found. Finally, 2 articles were included in this literature review, 1 case series of 6 adolescents[12] and 1 case report of a 10-year-old patient with DS [13]. ~~Both used the Inspire Medical System (Maple Grove, MN, USA).~~

The authors of the case report concluded that UAS therapy offers a promising treatment modality for the management of persistent severe OSA in the paediatric DS population, if the patients are carefully selected. However, further long-term study is on-going to evaluate the safety and efficacy of the UAS therapy over the first year after implantation of the device in this subject [13].

The case series evaluated the efficacy of UAS in 6 adolescents and young adults, aged 10-21 years old, with DS. Inclusion of the patients was based on the inclusion criteria used in prior studies of the UAS system in adult patients [8]. All patients had residual OSA after adenotonsillectomy and were CPAP intolerant. Follow-up polysomnography (PSG) showed a residual OSA in all patients but a decrease in OSA severity in all 6 patients was achieved, with a 56% to 85% reduction in apnea/hypopnea index (AHI) compared with baseline PSG. In addition, a mean use of 5.6 to 10.0 hours/night is reported. ~~Next~~ In addition to the improvement in AHI, the quality of life of the patients also improved significantly after implantation. Finally, the authors concluded that UAS represents a potential therapeutic option for patients with DS, but commented that further research is needed in order to optimise patient selection and to better assess the long-term clinical effectiveness of this therapy in this specific patient population~~icacy~~.

Case report

A 23-year-old male, diagnosed with DS and severe OSA, was referred to our centre . Unlike many adults with DS, this patient did not have other serious health conditions. He did not undergo any previous surgery except for a cholecystectomy. In the past, CPAP treatment was introduced with favourable results: a reduction in daytime sleepiness with some improvement in cognitive function. However, the parents deemed this treatment unfeasible since they had to readjust the nasal mask several times each night resulting in severe sleep fragmentation also for the parents. Other CPAP masks were fitted without any success. Before considering a non-CPAP treatment, a new baseline PSG was performed. The PSG showed a supine-dependent OSA with an AHI of 61.5 events/hour and an oxygen desaturation index (ODI) of 39.7 events/hour (table 1). A sleep position trainer (SPT) was prescribed hereafter in view of the positional dependency [14]. However, after a one month trial, the SPT treatment was discontinued due to intolerance [15]. In order to assess the surgical treatment options, a series of further investigations were performed. Ear, nose and throat examination revealed a normal nasal passage, grade 2 palatine tonsils, a normal sized uvula and a Mallampati score of 4. The body mass index (BMI) was 24.4 kg/m². Drug-induced sleep endoscopy (DISE), performed under sedation with midazolam and propofol [16], demonstrated an anteroposterior collapse of the velopharynx and tongue base, and a laterolateral collapse of the oropharynx and epiglottis. No collapse was present at the level of the hypopharynx. Subsequently, direct laryngoscopy excluded laryngeal anomalies. Based on the results of the clinical examination, the PSG and the DISE, the patient fulfilled the formal inclusion criteria for UAS therapy: AHI between 15 and 65 events/hour, BMI < 32 kg/m² and no complete concentric collapse during DISE. Implantation of the device (*Inspire II system, Inspire Medical Systems Inc., Maple Grove, MN, USA*) occurred uneventfully under continuous electromyogenic monitoring of the hypoglossal nerve [17]. The surgical technique has been described previously [18]. A postoperative chest radiograph confirmed the position of the pulse generator and excluded postoperative pneumothorax. Post operative titration and clinical follow-up took place according to a predefined protocol [19]. One month after implantation the UAS device was activated without discomfort at a stimulation amplitude of 1.0 V. Final titration occurred one month after activation during PSG to optimize therapeutic efficacy and patient tolerance by applying different stimulation levels. There was a clear difference in airflow and oxygen saturation with stimulation off compared to stimulation on (figure 2). Based on this titration PSG, with a residual AHI of 22.7 events/hour (63% decrease compared to baseline), the stimulation amplitude was elevated to 1.2 V. Average device usage amounted to 9.4 hours each night. Six months after implantation, an additional titration PSG was performed. However, no changes

Met opmerkingen [O1]: Partieel of volledig ?!?

Met opmerkingen [O2]: Idem

Met opmerkingen [O3]: Zoals ik al gezegd had, dient dit herwerkt te worden. IN deze zin moet de AHI gegeven worden tijdens dat deel van de titratienacht met de getitreerde amplitude en het bijhorende percentage delta AHI tov baseline. Nadien kan dan gezegd worden dat er een follow-up PSG was en dat daar het percentage daling 63% was. De range in de daling is dus tussen 63% en het andere percentage uit de titratienacht

were made because the patient did not tolerate any elevated voltage. The follow-up PSG showed a persistent response (table 1) with a 63% reduction in AHI and a 77% reduction in ODI.

	Baseline PSG	**Follow-up PSG at 6 months**
Sleep overview		
Total sleep time	6h 38min	7h 27min
Sleep efficiency *(%)*	75.6	84.5
REM sleep *(% sleep time)*	15.7	5.6
Respiration		
AHI *(events/hour)*	61.5	23.0
No. of apnea	221	13
No. of hypopnea	187	158
Snoring index *(events/hour)*	331.2	33.8
SaO_2		
ODI *(events/hour)*	39.7	9.3
Mean SpO_2 *(%)*	94.7	96.0
Minimal SpO_2 *(%)*	71.0	86.0
Position dependency		
AHI supine *(events/hour)*	92.7	41.2
AHI non-supine *(events/hour)*	22.7	20.2
Supine position *(% sleep time)*	65.0	13.0

Table 1.

Comparison of polysomnographic studies before and after device implantation.

PSG = polysomnography, REM = rapid eye movement, AHI = apnea-hypopnea-index, ODI = oxygen desaturation index, SaO_2 = oxygen saturation.

Met opmaak: Uitvullen, Regelafstand: Dubbel

Discussion

Down syndrome predisposes to OSA due to multiple anatomical variations, such as midfacial hypoplasia, relative macroglossia, glossoptosis, lingual tonsillar hypertrophy, hypotonia and lower airway stenosis [2]. Adults with DS have even more predisposing factors as they are more likely to develop obesity or hypothyroidism. DISE, performed in children with DS, revealed a multilevel collapse in 85% of patients [20]. As a consequence, these patients often require a combined approach including multilevel, surgical or nonsurgical treatments. One study described improvements in daytime functioning and excessive sleepiness in CPAP-compliant adults with DS and OSA [3]. However, no surgical treatments have been investigated so far in this population.

Respiration-synchronized UAS, using electrical neurostimulation of the hypoglossal nerve, reduces the collapsibility of the upper airway by activation of the genioglossus muscle [21]. This procedure may provide a multilevel effect without changing the anatomy [9]. Three components are implanted during the surgical procedure: an infraclavicular implantable pulse generator, a submandibular stimulation cuff-electrode around the protruding branches of the hypoglossal nerve (cranial nerve XII) and an intercostal sensing lead [19]. Since the hypoglossal nerve innervates both protrusion (genioglossus) and retraction (hyoglossus and styloglossus) tongue muscles, only the protruding medial branches are included in the stimulation electrode. Selective nerve monitoring facilitates the intraoperative identification of these different branches [17]. By sensing the pleural pressure, the device generates a respiration-synchronized stimulation of the hypoglossal nerve while sleeping. Long-term effectiveness and adherence of UAS therapy are well documented with the five-year results of the Stimulation Therapy of Apnea Reduction (STAR) trial recently published [8, 22, 23]. Serious adverse events are uncommon and side effects are generally well tolerated. Nevertheless, selecting suitable patients remains of paramount importance. Only patients who are non-compliant to CPAP treatment with moderate to severe OSA (AHI between 15 and 65 events/hour), are considered good candidates for UAS therapy. Exclusion criteria are as follows: obesity (BMI > 32 kg/m²), central sleep apnea (> 25% of total AHI) and complete concentric collapse at the level of the velopharynx during DISE [24, 10, 8, 19].

The application of UAS in DS patients has been described more recently in a paediatric and adolescent population [12]. The preliminary results of the first implant recipients were described previously [11]. All six subjects experienced a significant improvement in OSA (56% to 85% decrease in AHI) with a good tolerance of the treatment [8, 23]. In our case, the AHI decreased significantly (63% to 81%) ~~– comparable with the study of~~

~~Diercks et al. , but remained moderately elevated (23.0 events/hour) [8, 23]. This is also in accordance with the results described in the case series, where residual OSA was seen in all patients. In our patients, especially the number of apneas decreased after implantation (94% reduction), whereas the number of hypopneas only decreased by 16%.~~ The effect on ODI was ~~even more~~as significant with a decrease of 77% as compared to baseline. ~~The results show a residual supine dependent OSA in this patient, with an AHI in supine position of 41.2 events/hour in the supine position compared to an AHI of 20.2 events/hour in the non-supine position. The prevalence of positional OSA has been described in the population undergoing UAS implantation before and after surgery. These results showed a high prevalence of positional OSA before and under UAS therapy (61%) [25]. Nevertheless, the effect of the UAS treatment could have been higher if the patient would have been able to tolerate higher stimulation voltages and/or SPT would have been continued at the same time. Importantly however, t~~The parents reported a significant improvement in daytime sleepiness and cognitive performance of their son and even expressed their gratitude and satisfaction in a letter to the interdisciplinary medical team. Since the activation of the device the patient slept soundly at night and enjoyed his activities once again during the day.

In summary, the results in the reported patient are in concordance with the results described in literature on UAS in the paediatric and adolescent population with DS. Our results clearly illustrate the potential value of UAS therapy in well-selected DS patients with OSA refractory to conventional treatments such as CPAP. However, there is lack of large cohort studies, so further research in the ~~paediatric and adult~~ population of patients with DS and hypoglossal nerve stimulation is warranted~~needed~~.

Figure 1.

Search strategy

Figure 2.

Representative signal recording during polysomnography comparing UAS off (left panel) and UAS on (right panel) in het reported patient. Electrical neurostimulation of the hypoglossal nerve, synchronized with respiration, corresponds to the increase in the EMG signal. This example recording clearly illustrates UAS leading to a normalization of both airflow and oxygen saturation.

Abbreviations: upper airway stimulation – UAS; electromyography – EMG; electrooculography – EOG; electroencephalography – EEG; oxygen saturation – SaO2.

References

1. SE Parker, CT Mai, MA Canfield, R Rickard, Y Wang, RE Meyer, P Anderson, CA Mason, JS Collins, RS Kirby, A Correa, N National Birth Defects Prevention (2010) Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. Birth defects research Part A, Clinical and molecular teratology 88 (12):1008-1016. doi:10.1002/bdra.20735

2. M Maris, S Verhulst, M Wojciechowski, P Van de Heyning, A Boudewyns (2016) Prevalence of Obstructive Sleep Apnea in Children with Down Syndrome. Sleep 39 (3):699-704. doi:10.5665/sleep.5554

3. MS Trois, GT Capone, JA Lutz, MC Melendres, AR Schwartz, NA Collop, CL Marcus (2009) Obstructive sleep apnea in adults with Down syndrome. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 5 (4):317-323

4. IT Lott, M Dierssen (2010) Cognitive deficits and associated neurological complications in individuals with Down's syndrome. Lancet Neurol 9 (6):623-633. doi:10.1016/S1474-4422(10)70112-5

5. C Lal, DR White, JE Joseph, K van Bakergem, A LaRosa (2015) Sleep-disordered breathing in Down syndrome. Chest 147 (2):570-579. doi:10.1378/chest.14-0266

6. LJ Epstein, D Kristo, PJ Strollo, Jr., N Friedman, A Malhotra, SP Patil, K Ramar, R Rogers, RJ Schwab, EM Weaver, MD Weinstein, M Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep (2009) Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 5 (3):263-276

7. K Yoshida (1999) Elastic retracted oral appliance to treat sleep apnea in mentally impaired patients and patients with neuromuscular disabilities. The Journal of prosthetic dentistry 81 (2):196-201

8. PJ Strollo, Jr., RJ Soose, JT Maurer, N de Vries, J Cornelius, O Froymovich, RD Hanson, TA Padhya, DL Steward, MB Gillespie, BT Woodson, PH Van de Heyning, MG Goetting, OM Vanderveken, N Feldman, L Knaack, KP Strohl, ST Group (2014) Upper-airway stimulation for obstructive sleep apnea. The New England journal of medicine 370 (2):139-149. doi:10.1056/NEJMoa1308659

9. F Safiruddin, OM Vanderveken, N de Vries, JT Maurer, K Lee, Q Ni, KP Strohl (2015) Effect of upper-airway stimulation for obstructive sleep apnoea on airway dimensions. The European respiratory journal 45 (1):129-138. doi:10.1183/09031936.00059414

10. PH Van de Heyning, MS Badr, JZ Baskin, MA Cramer Bornemann, WA De Backer, Y Dotan, W Hohenhorst, L Knaack, HS Lin, JT Maurer, A Netzer, RM Odland, A Oliven, KP Strohl, OM Vanderveken, J Verbraecken, BT Woodson (2012) Implanted upper airway stimulation device for obstructive sleep apnea. Laryngoscope 122 (7):1626-1633. doi:10.1002/lary.23301

11. GR Diercks, D Keamy, TB Kinane, B Skotko, A Schwartz, E Grealish, J Dobrowski, R Soose, CJ Hartnick (2016) Hypoglossal Nerve Stimulator Implantation in an Adolescent With Down Syndrome and Sleep Apnea. Pediatrics 137 (5). doi:10.1542/peds.2015-3663

12. GR Diercks, C Wentland, D Keamy, TB Kinane, B Skotko, V de Guzman, E Grealish, J Dobrowski, R Soose, CJ Hartnick (2017) Hypoglossal Nerve Stimulation in Adolescents With Down Syndrome and Obstructive Sleep Apnea. JAMA otolaryngology-- head & neck surgery. doi:10.1001/jamaoto.2017.1871

13. SN Bowe, GR Diercks, CJ Hartnick (2017) Modified surgical approach to hypoglossal nerve stimulator implantation in the pediatric population. The Laryngoscope. doi:10.1002/lary.26808

14. JP van Maanen, KA Meester, LN Dun, I Koutsourelakis, BI Witte, DM Laman, AA Hilgevoord, N de Vries (2013) The sleep position trainer: a new treatment for positional obstructive sleep apnoea. Sleep & breathing = Schlaf & Atmung 17 (2):771-779. doi:10.1007/s11325-012-0764-5

15. J Beyers, M Dieltjens, C Kastoer, L Opdebeeck, AN Boudewyns, I De Volder, A Van Gastel, JA Verbraecken, WA De Backer, MJ Braem, PH Van de Heyning, OM Vanderveken (2018) Evaluation of a Trial Period With a Sleep Position Trainer in Patients With Positional Sleep Apnea. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine

16. A De Vito, M Carrasco Llatas, A Vanni, M Bosi, A Braghiroli, A Campanini, N de Vries, E Hamans, W Hohenhorst, BT Kotecha, J Maurer, F Montevecchi, O Piccin, G Sorrenti, OM Vanderveken, C Vicini

(2014) European position paper on drug-induced sedation endoscopy (DISE). Sleep & breathing = Schlaf & Atmung 18 (3):453-465. doi:10.1007/s11325-014-0989-6

17. C Heiser, B Hofauer, L Lozier, BT Woodson, T Stark (2016) Nerve monitoring-guided selective hypoglossal nerve stimulation in obstructive sleep apnea patients. The Laryngoscope 126 (12):2852-2858. doi:10.1002/lary.26026

18. C Heiser, E Thaler, M Boon, RJ Soose, BT Woodson (2016) Updates of operative techniques for upper airway stimulation. Laryngoscope 126:S12-S16. doi:10.1002/lary.26158

19. OM Vanderveken, J Beyers, S Op de Beeck, M Dieltjens, M Willemen, JA Verbraecken, WA De Backer, PH Van de Heyning (2017) Development of a Clinical Pathway and Technical Aspects of Upper Airway Stimulation Therapy for Obstructive Sleep Apnea. Frontiers in neuroscience 11:523. doi:10.3389/fnins.2017.00523

20. M Maris, S Verhulst, V Saldien, P Van de Heyning, M Wojciechowski, A Boudewyns (2016) Drug-induced sedation endoscopy in surgically naive children with Down syndrome and obstructive sleep apnea. Sleep medicine 24:63-70. doi:10.1016/j.sleep.2016.06.018

21. A Oliven, DJ O'Hearn, A Boudewyns, M Odeh, W De Backer, P van de Heyning, PL Smith, DW Eisele, L Allan, H Schneider, R Testerman, AR Schwartz (2003) Upper airway response to electrical stimulation of the genioglossus in obstructive sleep apnea. Journal of applied physiology 95 (5):2023-2029. doi:10.1152/japplphysiol.00203.2003

22. BT Woodson, KP Strohl, RJ Soose, MB Gillespie, JT Maurer, N de Vries, TA Padhya, MS Badr, HS Lin, OM Vanderveken, S Mickelson, PJ Strollo, Jr. (2018) Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes. Otolaryngol Head Neck Surg:194599818762383. doi:10.1177/0194599818762383

23. C Heiser, A Knopf, M Bas, C Gahleitner, B Hofauer (2017) Selective upper airway stimulation for obstructive sleep apnea: a single center clinical experience. Eur Arch Otorhinolaryngol 274 (3):1727-1734. doi:10.1007/s00405-016-4297-6

24. OM Vanderveken, JT Maurer, W Hohenhorst, E Hamans, HS Lin, AV Vroegop, C Anders, N de Vries, PH Van de Heyning (2013) Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. J Clin Sleep Med 9 (5):433-438. doi:10.5664/jcsm.2658

25. J Beyers, M Dieltjens, PE Vonk, MJ Ravesloot, M Willemen, JA Verbraecken, PH Van de Heyning, N de Vries, OM Vanderveken (2018) Prevalence and clinical significance of positional obstructive sleep apnea in patients treated with upper airway stimulation therapy. Sleep and Breathing