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Short-term results of upper airway stimulation in obstructive sleep apnoea patients: the Amsterdam experience

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Abstract

Objectives. This paper aimed to: retrospectively analyse single-centre results in terms of surgical success, respiratory outcomes and adverse events after short-term follow up in obstructive sleep apnoea patients treated with upper airway stimulation; and evaluate the correlation between pre-operative drug-induced sleep endoscopy findings and surgical success.

Methods. A retrospective descriptive cohort study was conducted, including a consecutive series of obstructive sleep apnoea patients undergoing implantation of an upper airway stimulation system.

Results. Forty-four patients were included. The total median Apnoea–Hypopnea Index and oxygen desaturation index significantly decreased from 37.6 to 8.3 events per hour ($p < 0.001$) and from 37.1 to 15.9 events per hour ($p < 0.001$), respectively. The surgical success rate was 88.6 per cent, and did not significantly differ between patients with or without complete collapse at the retropalatal level ($p = 0.784$). The most common therapy-related adverse event reported was (temporary) stimulation-related discomfort.

Conclusion. Upper airway stimulation is an effective and safe treatment in obstructive sleep apnoea patients with continuous positive airway pressure intolerance or failure. There was no significant difference in surgical outcome between patients with tongue base collapse with or without complete anteroposterior collapse at the level of the palate.

Introduction

Obstructive sleep apnoea (OSA) is the most prevalent sleep-related breathing disorder, caused by episodes of partial or complete obstruction of the upper airway during sleep. Currently, continuous positive airway pressure (CPAP) is the 'gold standard' therapy for moderate-to-severe OSA, but its non-compliance rate is often high as a result of poor tolerance and low acceptance.[1]

Alternative treatments to CPAP include mandibular advancement devices, positional therapy or upper airway surgery. The latter aims to improve upper airway patency in order to prevent obstruction during sleep. Conventional surgical approaches to the upper airway for treatment of moderate-to-severe OSA have mediocre results and are often painful, with potentially serious complications and side effects. Therefore, new surgical techniques, which are patient friendly, safe and have a high surgical success rate, are in high demand, especially in severe OSA patients with CPAP failure.

A recent development is hypoglossal nerve stimulation, also referred to as selective upper airway stimulation. Using unilateral stimulation, selective fibres, which are mainly innervating the tongue protrusors, are stimulated during every breathing cycle. Furthermore, by including the cervical spinal nerve 1 (C1), the hyoid bone is displaced in an anterosuperior direction during stimulation. Although stimulation activates the tongue protrusors, previous studies have also shown that the effect of upper airway stimulation is not limited to the level of the tongue base, but also improves upper airway patency at the level of the palate. It has been suggested that this multilevel effect is caused by palatoglossal coupling.[2]

Upper airway stimulation has been shown to be effective in improving objective respiratory parameters, such as the Apnoea–Hypopnea Index and oxygen desaturation index, and subjective symptoms related to OSA, such as excessive daytime sleepiness. Adequate patient selection is of paramount importance. Previous studies have shown that upper airway stimulation is effective in patients with an Apnoea–Hypopnea Index of 15–65 events per hour, a body mass index (BMI) of 32 kg/m^2 or less, a non-supine Apnoea–Hypopnea Index of 10 or more events per hour, less than 25 per cent central apnoeas and an absence of concentric collapse at the palatal level during drug-induced

Main Article

Dr P E Vonk takes responsibility for the integrity of the content of the paper

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sleep endoscopy.[3–13] Some studies have also shown a good response in patients with a BMI of 35 kg/m^2 or less.[4,7]

The US Food and Drug Administration approved this new form of upper airway surgery in April 2014. During the first years after Food and Drug Administration approval, this procedure was only performed in cases of patient-specific reimbursement or in a commercial setting. Since April 2017, costs for upper airway stimulation for a selective group of OSA patients with an Apnoea–Hypopnea Index of 30–50 events per hour and CPAP failure, or intolerance, have been reimbursed as part of the basic healthcare system in the Netherlands as well. Currently, this surgical procedure is only performed in two centres in the Netherlands. One of the two centres is Onze Lieve Vrouwe Gasthuis ('OLVG'), Amsterdam.

The primary aim of this study was to retrospectively analyse the single-centre results in terms of surgical success, respiratory outcomes and adverse events after short-term follow up in OSA patients treated with upper airway stimulation. The second aim was to describe pre-operative drug-induced sleep endoscopy findings, and evaluate whether patients with an isolated tongue base collapse prior to surgery had a higher chance of surgical success in comparison to OSA patients with complete collapse at both the tongue base and the retropalatal level.

Materials and methods

Study participants

We performed a retrospective descriptive cohort study, including a consecutive series of OSA patients undergoing upper airway stimulation, at the Department of Otorhinolaryngology – Head and Neck Surgery, OLVG, Amsterdam, the Netherlands, between January 2017 and April 2019. Patients were excluded if pre- or post-operative polysomnography data were not available.

The main criteria for implantation of the upper airway stimulation system were: an Apnoea–Hypopnea Index of 15–65 events per hour, a central apnoea index of less than 25 per cent of the total Apnoea–Hypopnea Index, a non-supine Apnoea–Hypopnea Index of less than 10 events per hour, a BMI of less than 32 kg/m^2, CPAP failure or intolerance, and the absence of complete concentric collapse at the level of the velum observed during drug-induced sleep endoscopy.

Drug-induced sleep endoscopy procedure and classification system

Drug-induced sleep endoscopy was performed by one experienced ENT resident (PEV) in a quiet out-patient endoscopy setting using propofol, to evaluate surgical treatment options. Sedation, and monitoring of blood pressure, electrocardiogram and oxygen levels, was managed by a trained nurse anaesthetist. The level of sedation was controlled by a target controlled infusion pump, using the methods described by Schnider *et al.* to calculate the effective dose.[14,15] Prior to the intravenous (IV) infusion of propofol, 2 cc lidocaine was given IV, and in the majority of patients glycopyrrolate (Robinul®) was given IV to prevent mucosal hypersecretion.

The velum, oropharynx, tongue base and epiglottis ('VOTE') classification system was used to report on the anatomical structures causing upper airway collapse. This classification system distinguishes between four different levels and structures that may be involved in upper airway collapse (i.e. velum, oropharynx, tongue base and epiglottis). Three categories were used to define the degree of obstruction: no obstruction, with a collapse of 50 per cent or less; partial obstruction, with a collapse of 50–75 per cent and typically with vibration; or complete collapse, with a collapse comprising more than 75 per cent of the upper airway lumen. Depending on the different site(s) involved in upper airway obstruction, the configuration may be anteroposterior, lateral or concentric.[16]

Implantation, activation and titration

Approximately one month after implantation, the device was activated during a consultation at the out-patient clinic of the Department of Otorhinolaryngology – Head and Neck Surgery. After activation of the device, patients gradually increase the stimulation amplitude to optimise both comfort and subjective effectiveness.

Two months post-operatively, a post-titration visit took place, consisting of a consultation and an in-laboratory titration using polysomnography to optimise therapeutic settings. Although the majority of patients only needed one titration night, a second titration night was indicated when the clinical laboratory technician was not able to titrate the therapy to an effective setting during the first titration night. This could be due to, for example, device-related issues or low sleep efficiency, which meant that sufficient titration was not possible. When a second titration night was needed, data collected during this night were used in our analysis. As respiratory parameters were collected during a titration polysomnography, the results used were from the portion of sleep when therapy was under therapeutic settings, also called the 'treatment Apnoea–Hypopnea Index'.

Ethical considerations

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1975. Data on study subjects were collected and stored in an encoded manner to protect personal information. For this type of study, informed consent was not required.

Definitions

Surgical success was defined according to Sher's criteria: a reduction in pre-operative Apnoea–Hypopnea Index of more than 50 per cent and a post-operative Apnoea–Hypopnea Index of less than 20 events per hour.[17] Patients who did not meet the criteria for surgical success after (advanced) titration are referred to as non-responders.

Obstructive respiratory events were analysed according to the American Academy of Sleep Medicine criteria. An obstructive respiratory event in adults was scored as an apnoea if there was a drop in the peak signal excursion by 90 per cent or more for a duration of at least 10 seconds. A hypopnea was defined as a decrease of airflow by 30 per cent or more during a period of at least 10 seconds, combined with oxygen desaturation of 3 per cent or more.[18]

Statistical analysis

Statistical analysis was performed using SPSS software (version 22; SPSS, Chicago, Illinois, USA). Quantitative data were reported as means and standard deviations, or as medians (and quartiles 1 and 3) when not normally distributed. In

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Table 1. Baseline characteristics

Parameter	Total*
Gender (M/F; *n*)	38/6
Age (mean ± SD; years)	58.5 ± 9.6
BMI (mean ± SD; kg/m^2)	27.2 ± 2.4
AHI (median (Q1, Q3); events per hour)	37.6 (30.4, 43.4)
ODI (median (Q1, Q3); events per hour ≥3%)	37.1 (28.4, 42.6)

*Total $n = 44$. M = male; F = female; SD = standard deviation; BMI = body mass index; AHI = Apnoea–Hypopnea Index; Q1 = quartile 1; Q3 = quartile 3; ODI = oxygen desaturation index

order to compare pre- and post-operative polysomnography values, a paired *t*-test was performed when data were normally distributed. A Wilcoxon signed-rank test was applied when data were not normally distributed.

In order to identify a possible correlation between surgical success and collapse patterns observed during drug-induced sleep endoscopy, patients were divided into two subgroups. The first subgroup consisted of patients with complete collapse of the tongue base with or without partial collapse of the palate. The second subgroup comprised patients with both partial or complete collapse of the tongue base, and complete collapse of the palate. A chi-square test was applied to compare the surgical success in both subgroups. A *p*-value of less than 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics

In total, 47 patients underwent implantation of an upper airway stimulation system between January 2017 and April 2019. Two patients did not want to undergo a titration night, and in one patient a titration night had not yet been performed because of a delayed healing process. Therefore, the results of 44 patients were included for analysis. Thirty-eight patients were male (86.4 per cent). The mean age was 58.5 ± 9.6 years, with a mean BMI of 27.2 ± 2.4 kg/m^2.

Patients had a pre-operative median Apnoea–Hypopnea Index of 37.6 (quartiles 1 and 3 = 30.4, 43.4) events per hour, a median supine Apnoea–Hypopnea Index of 45.8 (quartiles 1 and 3 = 34.1, 65.0) events per hour and a median non-supine Apnoea–Hypopnea Index of 26.2 (quartiles 1 and 3 = 17.5, 35.9) events per hour. The percentage of total sleeping time in the supine position was 26.9 per cent (quartiles 1 and 3 = 10.2, 51.2). The median oxygen desaturation index (oxygen desaturation index of 3 per cent or more) was 37.1 (quartiles 1 and 3 = 28.4, 42.6) events per hour. An overview of baseline characteristics can be found in Table 1.

Pre- and post-operative upper airway stimulation outcomes

Respiratory parameters

The total median Apnoea–Hypopnea Index significantly decreased from 37.6 (quartiles 1 and 3 = 30.4, 43.4) events per hour to 8.3 (quartiles 1 and 3 = 5.3, 12.0) events per hour ($p < 0.001$). Both the supine and the non-supine Apnoea–Hypopnea Index significantly decreased, from 45.8 (quartiles 1 and 3 = 34.1, 65.0) to 15.4 (quartiles 1 and 3 = 7.2, 27.8) events per hour and from 26.2 (quartiles 1 and 3 = 17.5, 35.9) to 5.2 (quartiles 1 and 3 = 2.4, 10.0) events per hour, respectively. A significant reduction in oxygen

Table 2. Pre- and post-operative polysomnography findings

Parameter	Pre-operative*	Post-operative†	*P*-value‡
AHI (events per hour)	37.6 (30.4, 43.4)	8.3 (5.3, 12.0)	<0.001
Obstructive apnoea index (events per hour)	11.8 (2.7, 18.9)	0.8 (0.0, 2.2)	<0.001
Supine AHI (events per hour)	45.8 (34.1, 65.0)	15.4 (7.2, 27.8)	<0.001
Non-supine AHI (events per hour)	26.2 (17.5, 35.9)	5.2 (2.4, 10.0)	<0.001
% of total sleeping time in supine position	26.9 (10.2, 51.2)	11.9 (0.0, 41.3)	0.021
Minimum oxygen saturation levels (%)	84.0 (81.0, 87.0)	88.0 (87.0, 90.0)	<0.001
ODI (events per hour ≥3%)	37.1 (28.4, 42.6)	15.9 (11.3, 21.6)	<0.001

Data are presented as median (quartiles 1 and 3). *$n = 44$; †$n = 44$. ‡$p < 0.05$ (Wilcoxon signed-rank test). AHI = Apnoea–Hypopnea Index; ODI = oxygen desaturation index

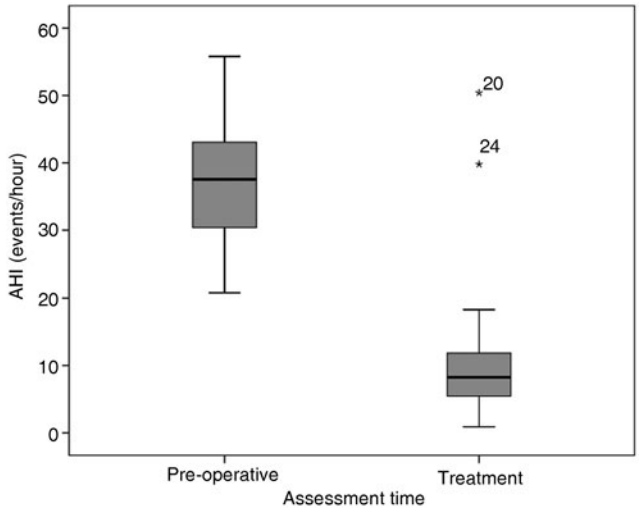

Fig. 1. Boxplot of the pre-operative versus treatment Apnoea–Hypopnea Index (AHI) scores. *Indicates outliers

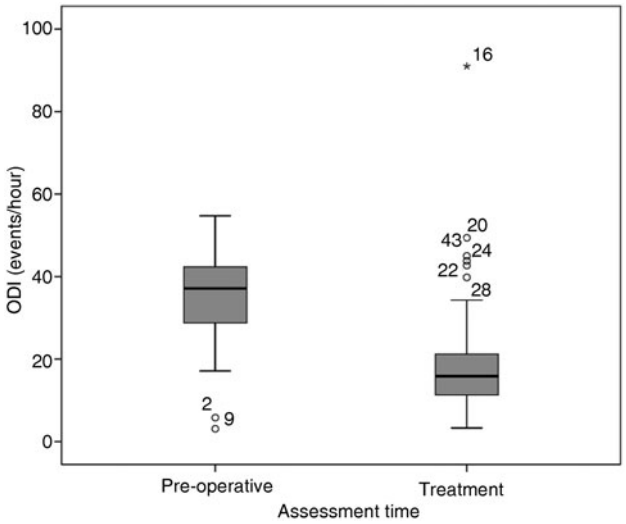

Fig. 2. Boxplot of the pre-operative versus treatment oxygen desaturation index (ODI) (3 per cent or more) scores. *Indicates outlier

desaturation index was also found, decreasing from 37.1 (quartiles 1 and 3 = 28.4, 42.6) to 15.9 (quartiles 1 and 3 = 11.1, 21.6) events per hour, as well as a significant increase in the

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Table 3. Pre-operative drug-induced sleep endoscopy findings*

Anatomical level	Configuration	Degree of collapse in supine position		
		No collapse (<50%)	Partial collapse (50–75%)	Complete collapse (>75%)
Velum	Anteroposterior	2	9	33
Oropharynx	Lateral	33	10	1
Tongue base	Anteroposterior	0	0	44
Epiglottis	Anteroposterior	2	4	36
	Lateral	0	1	1

Data represent numbers of cases. *Total $n = 44$

minimum oxygen. An overview of pre- and post-operative polysomnography parameters can be found in Table 2. Figures 1 and 2 show boxplots of the pre-operative versus the treatment Apnoea–Hypopnea Index, and the pre-operative versus the treatment oxygen desaturation index, respectively.

Surgical success

The surgical success rate in our study population was 88.6 per cent ($n = 39$). Reasons for not meeting Sher's criteria for surgical success were: a (temporary) increase of mixed and central apnoeas ($n = 1$), and the inability to perform a sufficient titration because of frequent awakening caused by the strength of the stimulation ($n = 3$). In one patient, proper titration of the therapy was not yet possible because of neuropraxia of the hypoglossal nerve after a post-operative bleed in the area of the neck incision.

Pre-operative drug-induced sleep endoscopy findings

In all patients, a complete anteroposterior collapse of the tongue base was observed during drug-induced sleep endoscopy. In 43 patients, an additional partial collapse ($n = 9$) or complete collapse ($n = 33$) at the level of the velum was observed. An isolated tongue base collapse was found in only one patient.

In the majority of patients with an epiglottic collapse, this was secondary to complete collapse of the tongue base. A floppy epiglottis was present in five patients. Partial or complete lateral collapse at the level of the oropharynx was less common. A detailed overview of collapse patterns can be found in Table 3.

As previously mentioned, 33 patients had complete collapse at multiple levels in the upper airway, consisting of a complete anteroposterior collapse of the palate and tongue base. When comparing differences in surgical outcome between patients with a complete multilevel collapse and patients with an anteroposterior tongue base collapse with or without a partial collapse of the palate, no significant difference in surgical success was found ($p = 0.784$).

Adverse events

In total, 26 patients reported therapy-related adverse events. Frequent awakenings or insomnia as a result of stimulation discomfort (affecting 45.5 per cent of patients) was the most common therapy-related adverse event reported. Post-operative bleeding and swallowing problems were both observed in one patient. In five patients, a revision of the sensor lead was needed, probably a result of damage to the sensor during implantation. Temporary tongue weakness was found in two patients, and tongue abrasion or a dry mouth was seen in eight patients. Table 4 provides an overview of patient-reported therapy-related adverse events.

Table 4. Therapy-related adverse events*

Parameter	Events (*n*)	% of total population
Post-operative bleeding	1	2.3
Revision interventions of sensor lead	5	11.4
Stimulation-related discomfort (including insomnia or arousal)	20	45.5
Infection	0	0
Tongue weakness or neuropraxia	2	4.5
Tongue abrasion, dry mouth	8	18.2
Problems with swallowing	1	2.3
Buzzing noise during stimulation	2	4.5
Total	39	

*In total, 26 out of 44 patients reported therapy-related adverse events

Discussion

This study aimed to retrospectively analyse the post-operative outcomes of upper airway stimulation treatment in patients with moderate-to-severe OSA with CPAP failure or intolerance. Upper airway stimulation significantly improved respiratory parameters. The overall surgical success rate in our study population was high, at 88.6 per cent. There was no significant difference in surgical outcome between patients with a tongue base collapse with or without a complete anteroposterior collapse at the level of the palate.

Our results are in line with those previously published in the literature. As part of the STAR (Stimulation Therapy for Apnea Reduction) trial, a 5-year follow-up study by Strollo *et al.* also found a significant reduction in Apnoea–Hypopnea Index (from 29.3 to 9.0 events per hour) and oxygen desaturation index (from 25.4 to 7.4 events per hour) in moderate-to-severe OSA patients 12 months after implantation, with a surgical success rate of 66 per cent.[10] These results were maintained during long-term follow up.[8,12]

Since Food and Drug Administration approval, several studies on the objective and subjective outcomes of upper airway stimulation treatment have been published. Heiser *et al.* reported a decrease in median Apnoea–Hypopnea Index, from 28.6 to 8.3 events per hour, after six months of follow up.[19] Boon *et al.* found similar results.[3] Specifically, regarding post-titration patient outcomes, there was a significant

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decrease in mean Apnoea–Hypopnea Index from 35.6 ± 15.3 to 10.2 ± 12.9 events per hour. The surgical success rate in that study was 78 per cent.[3] In another small-scale study by Kent *et al.*, post-titration Apnoea–Hypopnea Index also significantly decreased, and Apnoea–Hypopnea Index was reduced to within a normal range (Apnoea–Hypopnea Index of less than 5 events per hour) in 70 per cent of all patients.[5]

As stated above, our study found similar results. The higher surgical success rate in our study compared to the 12-month results of the STAR trial could be due to differences in follow-up length, and increased knowledge with regard to patient selection and titration since Food and Drug Administration approval. Nevertheless, one could argue that the decrease of the Apnoea–Hypopnea Index in our study was even greater than that reported in several previous published studies, as the baseline Apnoea–Hypopnea Index in our study population was higher (at 37.6 events per hour). The high baseline Apnoea–Hypopnea Index in this study population can be explained by the fact that, in the Netherlands, costs for treatment with upper airway stimulation are only reimbursed for patients whose Apnoea–Hypopnea Index lies between 30 and 50 events per hour.

- Upper airway stimulation is an effective alternative in moderate-to-severe obstructive sleep apnoea (OSA) patients with continuous positive airway pressure intolerance or failure
- Upper airway stimulation treatment significantly reduces objective respiratory parameters such as Apnoea–Hypopnea Index and oxygen desaturation index
- This treatment also significantly reduces excessive daytime sleepiness, measured with Epworth Sleepiness Scale
- Upper airway stimulation effects are not limited to tongue base level; treatment also improves upper airway patency at palate level
- Upper airway stimulation has proven effective in OSA patients with isolated retropalatal obstruction
- There were no differences in surgical success between patients with isolated tongue base collapse, or complete retropalatal and tongue base obstruction, observed pre-operatively during DISE

Although it must be taken into account that our sample for this analysis was small, no differences in surgical success were found when comparing patients with complete collapse of the tongue base with or without complete anteroposterior collapse at the level of the palate. This finding is supported by two previously published studies. Heiser *et al.* described the principle of palatoglossal coupling in patients treated with upper airway stimulation.[2] It was concluded that by selective stimulation of the hypoglossal nerve, more than 80 per cent of all implanted patients had both a significant opening of the upper airway at the retropalatal level and the level of the tongue base.[2] In another study, the post-operative results of patients with an isolated retropalatal collapse or multilevel collapse undergoing upper airway stimulation were compared. The post-operative results showed that the reductions in Apnoea–Hypopnea Index, success rate and cure rate were comparable between the two groups.[20]

Clinical relevance

Obstructive sleep apnoea is associated with an increased risk of developing cardiovascular disease, high morbidity and mortality. Some studies have also suggested that OSA is a risk factor for stroke, and an independent predictor of functional recovery and mortality in stroke patients.[21–24] In patients with moderate-to-severe OSA and CPAP intolerance, or CPAP failure, adequate OSA treatment is of paramount importance.

Many forms of upper airway surgery have been described in the literature. Many are hampered by low surgical success rates, and it is known that a high pre-operative Apnoea–Hypopnea Index is a negative predictor for surgical success. Patients selected for upper airway stimulation have often experienced failure of both conservative and surgical treatment for OSA. However, the surgical success rate of upper airway stimulation is higher compared to other types of upper airway surgery.[25] Proper patient selection, and adequate and specialised follow up by a team trained for this type of surgery, are key to treatment success.

Limitations

This study is not without limitations. First, this study contains data collected during a titration night, whereby, in the majority of included patients, an adjusted Apnoea–Hypopnea Index, also referred to as the treatment Apnoea–Hypopnea Index, was used for analysis. Second, interpretation of upper airway stimulation results is not only dependent on its effect on respiratory events, but also on its compliance.[26] The results of this study show that upper airway stimulation is an effective treatment in patients with moderate-to-severe OSA, but therapy usage is not taken into account. Hence, the results of this study could be an overestimation of treatment effectiveness when compared to an actual in-home situation. Long-term follow up of both objective and subjective outcomes, including therapy usage, is therefore required. Third, subjective outcomes were not included in this study. This was because of a lack of data, which would make analysis of such data unreliable.

Conclusion

Upper airway stimulation has proven to be an effective treatment for moderate-to-severe OSA patients with CPAP intolerance or failure, in terms of respiratory outcomes, with a surgical success rate of 88.6 per cent. There was no significant difference in surgical outcomes between patients with a tongue base collapse with or without a complete anteroposterior collapse at the level of the palate. The most common therapy-related adverse event reported was (temporary) stimulation-related discomfort, often leading to frequent awakenings or insomnia. Upper airway stimulation seems to be a promising alternative for moderate-to-severe OSA patients with CPAP intolerance or failure; however, proper patient selection, adequate implantation of the upper airway stimulation system and follow up by trained personnel are the key to treatment success.

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