Non-CPAP Therapies in Sleep Apnoea

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Abstract

**Background:** In view of the high prevalence and the relevant impairment of the patients with obstructive sleep apnoea syndrome (OSAS) lots of methods are offered which promise definitive cure or relevant improvement of OSAS.

**Question:** Efficacy of alternative treatment options in OSAS.

**Methods:** An interdisciplinaty ERS Task Force valuated the scientific literature according to the standards of evidence-based medicine.

**Results and answer:** Evidence supports the use of mandibular advancement devices in mild to moderate OSAS. Maxillomandibular osteotomy seems to be as efficient as CPAP in patients who refuse conservative treatment. Distraction osteogenesis is usefully applied in congenital micrognathia or midface hypoplasia. There is trend to improving under weight reduction. Positional therapy is clearly inferior to CPAP and long term compliance is poor. Drugs, nasal dilators, apnoea triggered muscle stimulation cannot be recommended as effective treatment of OSAS at the moment. Nasal surgery, radiofrequency tonsil reduction, tongue base surgery, uvulopalatal flap, laser midline glossectomy, tongue suspension, genioglossus advancement cannot be recommended as single interventions. Uvulopalatopharyngoplasty, pillar implants, hyoid suspension should only be considered in selected patients and potential benefits should be weighed against the risk of long-term side effects. Multilevel surgery is only a salvage procedure for OSA patients.

**Key-words:** Neuromuscular stimulation, positional therapy, weight reduction, mandibular advancement devices, maxillomandibular osteotomy, distraction osteogenesis, radiofrequency surgery, compliance, nasal dilators, nasal surgery, tongue base surgery, uvulopalatal flap, laser midline glossectomy, tongue suspension, genioglossus advancement, uvulopalatopharyngoplasty, pillar implants, hyoid suspension, multilevel surgery.
Introduction

Since the first description in the early 1980\textsuperscript{th} by Sullivan the application of continuous positive airway pressure (CPAP) and the more recent developments of automatic positive airway pressure (APAP) and bilevel therapy have become the standard treatment of the obstructive sleep apnoea syndrome (OSAS) \cite{1}. Positive airway pressure has proven to improve symptoms, normalize the risk of accidents in traffic and profession and reduce the elevated sympathetic activity, the risk for cardiovascular morbidities, especially arterial hypertension. Most recently, it has been shown that CPAP normalizes mortality in patients with severe OSAS \cite{2, 3}.

However, despite the efficacy of CPAP many patients suffer from local side-effects at nose or face or discomfort due to the mask. Moreover, CPAP does not allow for a permanent resolution of respiratory disturbances during sleep, but only suppresses them while using the devices. Therefore, many patients look for more comfortable or curative treatment options. Both conservative and surgical alternative therapeutical approaches have been described. However, there is a need to discuss the scientific evidence of these therapies.

Thus, the European Respiratory Society funded a Task Force with the aim to screen the scientific literature on non-positive-pressure therapies, to evaluate the studies according to the criteria of the evidence-based medicine, and to give recommendations for the use in OSAS patients. The treatment of central sleep apnea and periodic breathing was not in the focus of this work. The results of the Task Force will be presented in this report and in more detail in two following articles on conservative treatment options and two on surgical approaches.

Methods

The members of the Task Force performed individualized literature researches for each topic area using electronic data bases, hand searches of relevant papers, and screening of reference lists up to 1.1.2009. An additional search for most recently published papers which could relevantly change conclusions or recommendations was performed in May 2010. In addition in May 2010 the authors screened the literature for more recent papers which might change the conclusions and
Recommendations of the Task Force

1. There is a trend to worsening but not spontaneous cure of sleep disordered (C).
2. Weight reduction is associated with a trend to improvement in breathing pattern, quality of sleep, and daytime sleepiness and is recommended to reduce the important risk factor (C).
3. Positional therapy can yield moderate reductions in Apnoea-Hypopnoea-Index (AHI) (younger patients, low AHI, less obeses) but is clearly inferior to CPAP and therefore cannot be recommended except in carefully selected patients. Long term compliance with positional therapy is poor (C).
4. Apnoea triggered muscle stimulation cannot be recommended as an effective treatment of the obstructive sleep apnoea syndrome at the moment (negative recommendation, C). Although the tongue muscle training improves snoring, it is not efficacious in the treatment of sleep apnoea in general (negative recommendation, B).
5. Mandibular Advancement Devices (MAD’s) reduce sleep apnoeas and subjective daytime sleepiness and improve quality of life compared with control treatments are recommended in the treatment of patients with mild to moderate OSA (A). There is emerging evidence on beneficial cardiovascular effects from MAD’s. However, Tongue-retaining devices (TRD) cannot be recommended (C).
6. Drug therapy is not recommended as treatment for obstructive sleep apnoea (most drugs C, for mirtazapine and protryptilline B).

7. Nasal dilators are not recommended for reducing snoring, or for improving sleep-disordered breathing, or sleep architecture in obstructive sleep apnoea (D).

8. Nasal surgery as a single intervention cannot be recommended for treatment of obstructive sleep apnoea (negative recommendation, C).

9. Intranasal corticosteroids improve mild-to-moderate OSA in children with co-existing rhinitis and/or upper airway obstruction due to adenotonsillar hypertrophy (B). They may also show some benefit with respect to both symptoms and some sleep parameters. Intranasal corticosteroids can be recommended as concomittant therapy in these situations.

10. Tonsillectomy as a single therapy can be recommended for treatment of obstructive sleep apnoea in the presence of tonsillar hypertrophy in adults (C). Adenotonsillectomy can be recommended in the presence of adenotonsillar hypertrophy associated with pediatric obstructive sleep apnoea (C). Radiofrequency tonsil reduction is not recommended as a single procedure for the treatment of obstructive sleep apnoea (negative recommendation, D).

11. Uvulopalatopharyngoplasty (UPPP) is a single-level surgical procedure working only in selected patients with obstruction limited to the oropharyngeal area. When proposing UPPP, potential benefits should be weighed against the risk of frequent long-term side effects such as velopharyngeal insufficiency, dry throat, and abnormal swallowing. UPPP cannot be recommended except in carefully selected patients (C).

12. Laser assisted uvulopalatoplasty has not demonstrated any significant effect neither on OSA severity nor in symptoms or quality of life domains and is not recommended (negative recommendation, B).

13. Due to insufficient evidence radiofrequency surgery of the soft palate may only be considered in patients with mild disease refusing or not requiring CPAP as long as the individual anatomy appears suitable. It cannot be recommended except in carefully selected patients (C).

14. Uvulopalatal flap as a single intervention cannot be recommended for treatment of obstructive sleep apnoea (negative recommendation, C). Studies investigating the uvulopalatal flap with tonsillectomy for OSA show a significant improvement of the severity of OSA and quality of life and this combined intervention can be recommended in selected patients (C).
15. Pillar® implants may be considered in patients with mild to moderate OSA, who are suitable with regard to their overall physical condition (not or only moderately obese, no or small tonsils, no sign of retrolingual obstruction), if conservative approaches are not accepted by the patient. Pillar implants cannot be recommended except in carefully selected patients (B).

16. Due to insufficient evidence, radiofrequency surgery of the tongue base as an isolated or combined procedure cannot be recommended and may only be considered in selected patients intolerant to conservative treatment as long as the overall condition appears suitable (non- or only moderately obese patients with retrolingual obstruction) (C).

17. Due to insufficient evidence hyoid suspension cannot be recommended and may only be considered in carefully selected patients with CPAP failure and may be combined with other procedures in multi-level surgery (C).

18. Procedures such as laser midline glossectomy and tongue suspension (Repose®) have a little role as a single treatment option for obese patients with moderate to severe OSA and cannot be recommended. There are at present no data about their role in patients with mild disease (negative recommendation C).

19. Genioglossus advancement (GA) cannot be recommended as a single procedure for the surgical treatment of OSA (C).

20. Maxillo-mandibular advancement (MMA) seems to be as efficient as CPAP in patients with OSA who refuse conservative treatment, particularly in a young OSA population without excessive BMI or other comorbidities and is recommended in this circumstance (B).

21. Distraction osteogenesis (DOG) can be recommended in congenital micrognathia or midface hypoplasia (mandibular lengthening: B, midface advancement: C).

22. Multilevel surgery (MLS) cannot be recommended as a substitute for CPAP but a salvage procedure for OSA patients in whom CPAP and other conservative therapies failed. Surgical success of MLS for OSA is often unpredictable and less effective than CPAP (C).
1. Conservative non-CPAP treatment options
1.1. The natural course of sleep apnoea

Rationale
In the face of the high prevalence and the socioeconomic burden of OSAS the question arises if all patients have to be treated immediately after diagnosis or if spontaneous normalisation might be expected at least in a portion of patients.

Search strategy
Data bases individually searched: PubMed and Medline. Keyword combinations: Sleep apnoea AND progression OR natural course OR prognosis OR evolution OR long-term follow up. Of the selected papers, 24 studies reported data on the natural course of the disease.

Overview of the evidence
There is a lack of knowledge on the age of onset and the course of sleep apnoea. It is widely accepted that snoring typically begins between the age of 30 and 40 years, and that the incidence of sleep apnoea increases between 40 and 65. These data, however, do not reveal to the progression of the disorder with respect to its extent: neither concerning the apnoea hypopnoea index (AHI), nor clinical symptoms, nor comorbidity.

Only a small number of studies [3, 5-11] have investigated the natural course of sleep apnoea with respect to cardiovascular risk and mortality. The studies cited here monitored those patients who refused to undergo appropriate therapy. A small number of studies has been performed investigating the course of the disease in patients with low AHI figures. No long-term follow-up studies have been performed on sleepiness, the primary symptom of OSA.

The present state of knowledge on this matter considering only those follow-up studies with more than 20 participants can be summarised as follows: Tishler et al. studied healthy persons (i.e., AHI <5) and found a 5-year incidence of 7.5% for OSA with an AHI >15, and of approximately 16% with AHI >10. The incidence of sleep apnoea was independent of age, gender, body mass index (BMI), waist-hip radio, and serum cholesterol level. Interestingly, the influence of BMI diminished with
increasing age [12]. The Wisconsin Sleep Cohort Study and the Cleveland Family Study revealed a significant increase over the time in AHI, especially among male, obese, older, and snoring patients [13, 14]. Studies in elderly revealed a progression of OSA in correlation with age over the long term, but not with BMI [15]. The Sleep Heart Health Study found that the increase of the AHI upon an increase of the BMI over 5 years was greater than a reduction of AHI under weight loss. The influence of body weight was significantly greater among men than among women [16]. In addition, Peppard et al. reported a 6-fold increase in odds ratio (OR) for the development of OSA, as accompanied by a 10% increase in body weight within 4 years [17].

There are conflicting results on the modulation of the severity of OSAS over the time. While several investigators showed an increase of the severity in mild to moderate sleep apnoea patients over the time independently of the BMI, others failed to demonstrate deterioration of upper airway resistance syndromes or found improvements of respiratory disturbances [5, 18-24].

Conclusions and recommendations
There is a lack of population-based studies on the spontaneous course of OSA. However, both increasing incidence and progression of AHI have been evidenced for patients with mild to moderate OSA between the ages of 40 and 60 years, even independently of possible change in BMI. In contrast, a similar evolution has not been proven among the elderly and among those patients with higher initial AHI. In all age groups, however, the primary risk factor for progression and elevated incidence is the increase of body weight. An additional factor is evidently male gender.

At least in mild SRBD future research should address the influence of concomitant diseases and their therapy on the course of sleep apnoea, the significance of snoring with respect to the development from snoring to sleep apnoea, development of cardiovascular risks in snorers and sleep apnoea (Table e1).
Presented data show a trend to worsening of sleep disordered breathing over time. Most studies are retrospective and observational (case series). Based on these data we state that a spontaneous improvement cannot be expected (C).

1.2. Weight reduction

Rationale
Obstructive SRBD are caused by pharyngeal and/or laryngeal collapse. Pharyngeal fat deposits lead to a decrease in pharyngeal patency and underline the risk factor of obesity [25, 26]. Weight reduction will lead to a decrease in critical closing pressure (Pcrit), and consequently decreases the severity of OSA [27].

Search criteria
Data bases individually searched: PubMed and Medline. Keyword combinations: Sleep apnoea syndromes AND weight reduction. Of the 47 selected papers, 3 studies reported data on the mechanisms of action of weight reduction (change in critical closing pressure, change in pharyngeal cross-sectional area, change in respiratory mechanics).

Overview of the evidence
51 studies were identified, reporting on the effect of weight reduction in adults, 25 on diet instructions, 24 on surgical intervention (1 study evaluated both) and 3 on pharmaceutical weight reduction. 1 study performed in extremely overweight adolescents was also included [28]. Six studies were published by the same study group. 17 studies on diet instructions intervention were case series, or evidence level 4. Surgical treatment (gastric banding, gastroplasty, gastric bypass) was evaluated in 24 studies, all case series as well. Pharmaceutical weight reduction was reported in 2 case series in the same population and in 1 randomised controlled trial. Only studies with sibutramine were performed. 10 studies were based on polygraphy (7 diet studies, 3 surgery studies, 1 both). 7 of these polygraphic studies were performed in Finland. Weight changes have been calculated partly as change in kg, partly as change in BMI, partly as change in excess body weight (EBW) (and expressed as percentage EBW) or as change in %ideal body weight (IBW). Therefore, an overall change in body weight related to change in AHI cannot be expressed (Tables e2, e3).
In the diet intervention studies, mean BMI reduction of $4.7 \pm 2.5$ kg/m$^2$ was accompanied by a decrease of the AHI by $21 \pm 13$/h (44%) (Table e2). 246 patients (39%) showed a partial improvement in AHI, while 145 patients (23%) were cured from OSA. In the surgery intervention studies, change in BMI was between 10 - 24.4 kg/m$^2$. 3 studies reported reduction of the %IBW between 26.4 and 82 %IBW (17-73%) The AHI decreased by $44 \pm 22$/h (77%). [29-31] (Table e3). 94 patients (34.2%) showed a partial improvement in AHI, while 177 patients (64.4%) were cured from OSA. In the pharmaceutical intervention studies, change in BMI was between 1.8 and 2.6 kg/m$^2$, accompanied by a decrease of the AHI between 2.8 and 16.3/h (7-35.6%). [32-34] (Table e4)

An increase in deep sleep could be observed from $+4$ to $+17\%$, while other studies found no change in deep sleep or even a small decrease [35]. In all but one study REM-sleep increased with 1-10%. An improvement of sleepiness based on self-assessment scales was reported after diet and behavioural management, and after surgery, and after pharmaceutical weight reduction [31-41]. In one study an unchanged mean MSLT was reported [41]. The evaluated study period was not always indicated, the longest study period was 7 years [40].

**Conclusions and recommendations**

Presented data show under a weight reduction (BMI 0.2-24.4 kg/m$^2$) a trend to improvement in breathing pattern, an increase in REM sleep (1-10%) and deep sleep (0 to $+17\%$) and a decrease in daytime sleepiness. Most studies are retrospective and observational (case series), while randomised controlled trials have been published last years, but report inconsistent results and therefore none provide high-level evidence. Weight reduction is recommended to reduce the important underlying risk factor of obesity. Since most available studies have level 4 (C).

**1.3. Positional therapy**

**Rationale**

The number and duration of respiratory disturbances depend on body position and sleep stage [42-46]. The cross-section and the closing pressures of the pharynx differ according to body position and stage of sleep [47-49]. Ventilatory drive is dependent
on body position. Thus, there is ample evidence suggesting a positive effect of a lateral position during sleep. Using the definition of positional OSA as a supine AHI of at least twice that in the lateral position, a prevalence of approximately 50% is reported [50].

**Search criteria**

Data bases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea AND positional therapy. A recent review on medical therapy of OSA was screened. 27 of the 39 articles found were excluded mostly because they did not contain data on the efficacy of positional therapy in the treatment of OSA (Table e5).

**Overview of the evidence**

Clinical experience and observational studies suggest that the patients exhibiting a large decrease in AHI in the lateral position as compared to the supine position tend to have a lower AHI, to be younger and to be less obese [44, 51]. Accordingly, patients with a clear improvement of the AHI with positional therapy tended to be younger, to have a lower AHI and to be less obese [42, 52, 53]. It is not possible to extract from the data whether AHI, age or obesity is the best predictor of treatment success. It is more likely that these parameters are mutually interrelated.

Different devices such as a tennis ball, vests, positional alarm, verbal instruction and pillows are used to avoid the supine position [53-58]. There are no data comparing the different devices with the exception that verbal instructions seem to be less effective as compared to positional alarm [42, 59].

A number of short term studies demonstrate significant but moderate effects on AHI. However, most studies were uncontrolled and small [52-54, 56, 57, 60]. More importantly, even in a subset of patients with clear positional sleep apnoea effectiveness was limited. Two uncontrolled studies suggested some improvement of sleep stages or daytime symptoms with positional therapy [57, 58].

One study had a clinical meaningful follow up period of 2 years [56]. Only 29% used the positional vest in this study after 2 years [56]. In a randomised crossover...
comparison with CPAP, positional therapy (elevation of head and shoulder) was clearly inferior in terms of the AHI [61].

**Conclusions and recommendations**

Patients with a clear improvement of the AHI with positional therapy tend to be younger, to have a lower AHI, and to be less obese. Positional therapy can yield moderate reductions in AHI but is clearly inferior to CPAP. Long term compliance with positional therapy is poor. If positional therapy is used, sleep studies are recommended to document individual success. Long term compliance has to be secured by follow up studies.

Recommendation: Positional therapy is not recommended for the treatment of OSA except carefully selected patients. If positional therapy is used, sleep studies have to be performed to document individual success. Long term compliance has to be secured by follow up studies. (C).

**1.4. Intraoral protrusion devices**

**1.4.1. Mandibular advancement devices**

**Rationale**

Mandibular advancement devices (MAD’s) reposition the lower jaw forwards and downwards during sleep. The treatment aims to widen the upper airways in order to improve the upper airway patency and reduce snoring and obstructive sleep apnoeas.

**Search strategy**

Data bases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea syndromes AND orthodontic appliances; functional or removable, activator appliances or mandibular advancement, sleep apnoea AND oral appliances, mandibular advancement devices, mandibular repositioning appliances, mandibular advancement splints or mandibular repositioning splints were individually used. Out of 79 articles in total, 29 were excluded because the topic was covered in the RCT’s or the aims were not directly related to the efficacy of the device. 27 RCT’s about treatment effects from MAD’s and 5 RCT’s in particular topics were found.
(Table e6). In addition, 18 other clinical trials that highlighted particular aspects of MAD treatment were identified.

**Overview of the evidence**

The 27 RCT’s evaluated the effects from MAD’s compared with placebo-treatment [62-70], CPAP [66, 69, 71-77] or between appliance designs [78-87]. Two studies reported long-term results after 2 and 4 years treatment, respectively [86, 88]. The sample sizes in these studies ranged in between 17 and 114 patients. The patients were overweight or obese (mean BMI in between 26 and 33 kg/m²).

MAD’s have been shown to widen primarily the lateral parts of the upper airway [89] and to reduce the pharyngeal collapsibility [90]. MAD treatment reduced sleep apnoeas compared with placebo in all studies [62-66, 68-70]. Treatment success with MAD defined as an AHI of <5 was found in between 19 and 75% of the patients and an index of <10 was reported in between 30 and 94% of the patients [63-68, 70-79, 81, 82, 84, 85, 87, 91, 92]. Sleep apnoeas increased slightly and some patients discontinued treatment in the longer term [86, 88]. Milder sleep apnoea, supine-dependent sleep apnoeas, female gender and less obesity have been related to treatment success with MAD’s [63, 65, 70, 76, 82, 92, 93]. CPAP reduced sleep apnoeas more efficiently or gave a higher success rate in all studies[66, 69, 71-77].

Subjective daytime sleepiness decreased from MAD treatment compared with placebo according to many short-term studies [62, 64, 66, 68, 70], although control treatment may also give positive effects [64, 69]. The effect on sleepiness was usually similar between CPAP and MAD’s [66, 72, 74-77], but CPAP may produce a better outcome than MAD [69, 71, 73]. Snoring is more effectively controlled with CPAP than with MAD’s [72], but there is a better effect from MAD’s than placebo [63, 64]. Persistent snoring during MAD treatment may be a sign of a poor apnoea control [71]. Promising effects on blood pressure, cardiac function, endothelial function, markers of oxidative stress and simulated driving performance have been reported from MAD’s [66, 69, 84, 94-99].

Titrable custom-made MAD’s have been used in the majority of the efficacy studies. Comparison between device designs indicated that there are only minor differences
in treatment effects between custom-made devices [78, 80, 83, 84], while a prefabricated device was less effective [85]. The degree of mandibular advancement is crucial, since a non-advanced device is ineffective on sleep apnoeas [62, 65, 70] and may even increase the apnoea frequency [62]. A titration procedure is therefore recommended to achieve optimal results [87, 91, 100, 101].

Initial side-effects such as jaw discomfort, tooth tenderness, excessive salivation and/or temporary occlusal changes were reported in slightly more than half of the patients [63, 65, 69, 71-74, 78], and more frequently from MAD than from a control plate [64]. After one year 76% of the patients continued treatment [92] and 65% were still using their devices after 4 years [88]. Compliance monitors have been introduced [102]. Compliance with MAD has been reported to be higher than with CPAP [66, 77] and MAD´s are often preferred by the patients [71, 72, 74, 75, 77].

**Conclusions and recommendations**

MAD´s are recommended for the treatment of patients with mild to moderate OSA (A) and in patients who do not tolerate CPAP. MAD´s reduce sleep apnoeas and subjective daytime sleepiness and improve quality of life compared with control treatments. There is emerging evidence on beneficial cardiovascular effects from MAD´s. CPAP more effectively reduces sleep apnoeas, while the positive effects on symptoms and health are more similar between these treatments. The patients generally prefer MAD´s over CPAP. The device should be custom-made, evaluated and advance the mandible at least 50% of maximum protrusion. A titration procedure is essential. Re-evaluation with a new sleep apnoea recording is necessary, since the improvement of OSA-symptoms is an imprecise indicator of treatment success. This is particularly important in patients with a more severe disease and in patients with concomitant health problems. Follow-up should be performed regularly long term.
1.4.2. Tongue retaining devices

Rationale
Tongue-retaining devices (TRD’s) are designed to produce a suction of the tongue into an anterior bulb, move the tongue forwards and widen the upper airway dimensions during sleep in order to reduce obstructive sleep apnoeas and snoring.

Search strategy
Data bases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea AND tongue retaining device or tongue stabilizing device were individually used for searches in PubMed. In total, 3 RCT’s [59, 103, 104] and 3 other trials with small sample sizes were found [105-107] (Table e7).

Overview of the evidence
The three RCT’s [59, 103, 104] evaluated the effects from TRD’s on sleep apnoeas and symptoms and analysed predictors (Table e7). One RCT showed significant effects from TRD on sleep apnoeas compared with a control device in patients with mild to moderate sleep apnoea [103]. A comparison between a tongue stabilizing device (TSD) and MAD in another RCT showed a similar apnoea reduction from the two devices, although the patients preferred MAD’s [104]. TRD was compared with posture alarm and positional treatment in 60 patients with positional-dependency and moderate OSA. TRD reduced sleep apnoeas in the supine position and gave some benefit for patients who continued to sleep in that position [59]. One of the clinical trials showed an effect of TRD on oxygen desaturations [106], while the other two studies did not show any reduction in sleep apnoeas from this type of treatment in small samples of moderate to severe sleep apnoea patients [105, 107].

Conclusions and recommendations
TRD’s are not recommended for patients with OSA. They can be used in selected patients with mild to moderate OSA (C), when other treatments have failed or are not possible. These patients may have a trial with this device provided that the treatment effect is monitored and the patients are strictly followed-up. A few studies show reductions in sleep apnoeas from TRD’s, although symptomatic effects are mainly unknown and compliance might be a limitation.
1.5. Training of the upper airway muscles and hypoglossus nerve stimulation

Rationale

The obstruction of the upper airways is accompanied by diminished neuromuscular activity of the dilating muscles [108]. In healthy subjects these muscles stabilize the pharyngeal airway. In order to counterbalance the collapsible forces, the upper airway muscles have to contract more intensively [109]. The genioglossus muscle is one of the most important dilators which pushes forward the tongue and enlarges the cross-sectional area of the upper airways. Its activity is increased in OSAS during wakefulness, which has been proposed to be a compensatory mechanism [110, 111]. Based on these findings the question arose, whether direct or indirect stimulation of the upper airway muscles optimize the dilating forces and increases the width of the upper airways. Present development focus mainly on hypoglossus nerve stimulation. Electrical stimulation is performed during sleep to counteract respiratory disturbances whenever they appear. On the other hand, training procedures have been developed aiming at improving the altered upper airway muscles. These training procedures are performed during wakefulness.

Search criteria

Data bases individually searched: PubMed. Keyword combinations: neurostimulation OR electrical stimulation OR upper airway muscles OR genioglossus stimulation OR hypoglossus nerve stimulation AND sleep apnoea syndrome. 28 studies were found of which 13 were included in the further evaluation. The other studies did not focus on the electrical stimulation of the upper airway muscles, but on physiological or pathophysiological aspects, effects of mandibular advancement devices or drugs on the upper airway muscles or surgical or anaesthesiological aspects (Table e8).

Overview of the evidence

Acute efficacy of electrical stimulation on the upper airway patency

Stimulation of the upper airway muscles with surface and intraneural electrodes has proven to reduce the resistance of the upper airways both in healthy persons and patients with OSAS [27, 112-118]. The stimulation of the genioglossus muscle most effectively reduces resistance and the critical pressure (Pcrit) [113, 115, 116].
Efficacy of apnoea-triggered neurostimulation in clinical use
There are conflicting results on the clinical efficacy of apnoea-triggered neurostimulation. Intraneural stimulation of the hypoglossus nerve and transcutaneous electrical stimulation of the genioglossus muscle showed significant improvements of respiratory disturbances and sleep parameters without adverse effects [112, 119]. In contrast, other groups failed to find an enlargement of the upper airways by transcutaneous or intramuscular stimulation during wakefulness or sleep. However, undesirable contractions of the platysma or tongue were observed and arousals were induced [114, 116, 120, 121]. Oliven et al. studied the critical pharyngeal pressure under intraneural hypoglossus and intramuscular and surface genioglossus stimulation [115, 116] and demonstrated that the patency of the upper airways depends more on the effective stimulation of the genioglossus muscles [115].

Tongue muscle training by electrical stimulation
Electrical stimulation has proven to be effective in the rehabilitation of skeletal muscles after injury. It activates motor units in healthy muscles, which cannot be reached voluntarily. Based on these findings the question arises if training of the pharyngeal muscles, especially the genioglossus muscle, during the daytime might improve the respiratory disturbances during sleep. Preliminary results of case studies and one cohort showed improvements of the AHI, daytime sleepiness and snoring [122, 123]. The only placebo controlled double blind study on tongue muscle training found an improvement of snoring but no significant reduction of the AHI [124].

Oropharyngeal exercise
In addition to electrical stimulation of the upper airway muscles it has been studied if exercises may improve symptoms of OSAS. Puhan et al. showed a reduction but not normalization of the AHI under didgeridoo playing [125]. More recently, Guimarães et al. randomized 31 patients with moderate OSAS to three months of oropharyngeal exercises or sham therapy. They found significant but limited reduction of the AHI. Moreover, snoring, daytime sleepiness, neck circumference and self-assessment questionnaires demonstrated improvements. It is unclear which of several exercises was most relevant for the treatment effect [126].
Conclusions and recommendations
Apnoea triggered muscle stimulation cannot be recommended as an effective
treatment of the obstructive sleep apnoea syndrome at the moment (C). Although
oropharyngeal exercise has shown limited effects on snoring and respiratory
disturbances, its role is not clear at the moment and therefore cannot be
recommended by now (B).

1.6. Drug therapy
1.6.1. Neuromediator modulators

Rationale
Although there may be a predisposing airway abnormality, it is changes in respiratory
drive, airway tone or surface forces that cause airway closure during sleep.
Pharmaceutical agents might reduce sleep apnoea by increasing respiratory drive,
changing sleep structure (in particular suppressing REM sleep), increasing upper
airway muscle tone, changing respiratory and cardiovascular reflexes that may
perpetuate apnoeas and reducing surface forces that encourage closure of the upper
airway.

Search strategy
Data bases individually searched: PubMed and Medline. Keyword combinations:
Sleep apnea/ apnoea (drug* or pharmacological and (treatment*)) or progesterone or
progestogen or medroxy* or "tricyclic anti depressant**" or protriptyline or amitriptyline
or imipramine or ssri or fluoxetine or clonidine or modafinil or stimulant* or Buspirone
or doxapram or dopram or naloxone or narcan or "opiod antagonist**" or nicotin* or
"ACE inhibitor**" or ACE-inhibitor* or cilazapril or captopril or enalapril or fosinopril or
imidapril or lisinopril or perindopril or quinapril or ramipril or trandolapril or "anti
hypertensive**" or anti-hypertensive* or antihypertensive* or baclofen or mirtazapine
or steroid* or *steroid or fluticasone

Reports on snorers or subjects with predominantly central apnoeas were excluded.
Even with these filters a large number of low quality studies were identified. For
nearly all of the drugs that have been trialled in the last 20 years there is at least one
randomised controlled trial (RCT) and so uncontrolled studies and review articles were excluded.

**Overview of the Evidence.**
Twenty-five studies (24 papers) were identified, reporting the effects of 24 drugs and recruiting between them 413 subjects. Due to small size, a lack of detail in reporting the methods in particular randomisation and incomplete data few of the studies scored higher than 2b as a level of evidence. Three studies included protriptyline, their results were subjected to meta-analysis and scored as 1a (Table e9) [127].

Protriptyline is a tricyclic antidepressant that inhibits re-uptake of serotonin and noradrenaline. It might reduce the proportion of REM sleep in people with REM predominant OSA and increase the airway tone mediated by serotonin acting on genioglossus via the hypoglossal nerve. However, there was no impact on the respiratory indices but there was an improvement in daytime symptoms in two out of three trials presumably due to a non-specific alerting effect of the drug. Adverse side effects such as dry mouth and urinary symptoms were commonly reported. Protriptyline does not have any place in the routine treatment of OSA [128-130].

Specific serotonin re-uptake inhibitors such as paroxetine have been investigated as possible treatments for OSA. In a small single night study, paroxetine 40 mg had no impact on AHI compared to placebo with severe OSA [131]. By contrast in a study with 6 week treatment arms paroxetine 20 mg was shown to reduce AHI to 23.3 compared to 30.3 for placebo. There was a positive impact on respiratory events in non REM but no effect in REM sleep and no improvement in daytime symptoms [132].

Mirtazapine is another drug with antidepressant activity that acts as an agonist at some serotonin receptors and can also increase serotonin secretion. This might increase serotonergic tone to the hypoglossal nerve, which could be particularly helpful during REM sleep. Reductions in the AHI were reported in one study [133] but could not be reproduced in two multi-centre trials, while many participants reported side effects of sleepiness and weight gain [134]. The drug cannot be recommended for use in OSA.
Cholinergic agonists have been investigated as possible treatments for OSA. On a single night study 10 subjects had an AHI of 41 on physostigmine compared to 54 on placebo [135]. The greatest impact was on apnoeas during REM sleep and there was an inverse relationship with BMI such that slimmer subjects had a greater fall in AHI. The drug was given intravenously making it impractical for home use. There have been no studies with oral cholinergic agents.

Acetazolamide inhibits carbonic anhydrase producing a metabolic acidosis that increases ventilatory drive. It was shown to reduce the AHI in a study of 10 subjects but there was no positive impact on daytime symptoms after one week of treatment [130]. The subjects who had responded best to the drug were offered a more prolonged trial of treatment but only one could tolerate it in the long term. It has no role in the routine management of OSA.

On a single night study with 10 subjects, phosphocholinamin was given as a topical nasal lubricant administered twice overnight which resulted in an AHI of 14 compared to 24 with placebo [136]. In view of the duration of the study it is not known whether this might improve daytime symptoms but the drug was not recommended for long term use due to anxiety about aspiration causing lipoid pneumonia. There are no published studies of any other candidate substances.

Among the other drugs that have been trialled, naltrexone, theophylline and aminophylline have been shown to reduce the number of respiratory events overnight but this was at the expense of sleep continuity and total sleep time which makes them unsuitable agents for the treatment of OSA. Omeprazole has been said to reduce the frequency of attacks of apnoea in subjects who had both OSA and gastro oesophageal reflux disease but no sleep studies were performed on treatment and the attacks may well have been episodes of laryngospasm due to acid reflux not episodes of OSA. Medroxyprogesterone, doxapram, clonidine, mibefradil, cilazapril, buspirone, ondansetron and sabeluzole have all been investigated and none has been shown to reduce the frequency of respiratory events in people with OSA or to improve daytime symptoms.
Conclusions and recommendations
At the present time there is no evidence that any drug is likely to benefit an unselected patient with OSA. Small studies have reported positive effects of certain agents on short-term outcomes. Longer studies with measures of symptomatic responses of cholinergic agents and upper airway lubricants are supported by the results of single night studies already published. It is likely that better characterisation of the predominant mechanisms of OSA in individual patients will lead to better results and this also needs further study. Drug therapy is not recommended as treatment for obstructive sleep apnoea (most drugs C, for mirtazapine and protryptilline B).

1.6.2. Nasal Steroids

Rationale
A particularly frequent cause of nasal obstruction is allergic rhinitis, either seasonal or perennial. There are a number of reports suggesting worsening of subjective sleep quality and quality of life measures in both adults and children with allergic and perennial rhinitis [137]. Vice versa, Canova and co-workers [138] demonstrated an increased prevalence of perennial allergic rhinitis in patients with OSA (11%) compared to case-controls (2.3%). In addition to the obstructing effects of allergic rhinitis, inflammation of the nasal mucosa may contribute to the development of adenotonsilar hypertrophy, one of the most frequently observed abnormalities in children with OSA. Intranasal corticosteroids are commonly used to treat rhinitis. A recent Cochrane review on intranasal corticosteroids showed significant efficacy of intranasal corticosteroids in improving nasal obstruction symptoms and in reducing adenoid size [139]. Consequently, this may influence the anatomic component by decreasing upper airway resistance at the nasal, adenoidal, and/or tonsillar levels. Therefore, topical nasal steroids may influence sleep apnoea severity both in children and adults.

Search criteria
Data bases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea and intranasal corticosteroids, sleep apnoea and inhaled corticosteroids, sleep apnoea and intranasal steroids, sleep apnoea and
corticosteroids, nasal steroids and sleep apnoea, sleep apnoea and fluticasone, sleep apnoea and triamcinolone, sleep apnoea and budesonide, OSAS and corticosteroids.

Overview of the evidence
We identified only one single-centre study with a small sample size that investigated the effects of intranasal corticosteroid application for 4 weeks on polysomnographically diagnosed sleep parameters in adult patients with moderate OSA and co-existing (perennial or seasonal) rhinitis [140]. There was a modest but significant decrease in AHI and an improvement in nasal airflow resistance, however, there were no significant improvements in oxygenation indices, sleep quality or snoring noise.

Five studies with a total of 136 children (age range 1-14 yrs) with mild to moderate OSA were identified. 2 studies were conducted as open clinical trials without a control group, 1 study investigated the effects of budesonide and Montelukast, using a case control design, and 2 studies were conducted as prospective, randomised, placebo controlled trials. Most of the children included in these reports had evidence of co-existing rhinitis with or without adenotonsillar hypertrophy. All included reports observed significant treatment associated improvements in the AHI (mean pre-treatment AHI range 3.7–11 vs. treatment associated mean AHI range 0.3–6). Three reports furthermore showed significant improvements in oxygenation indices and two studies demonstrated improved sleep quality. The data are, however, inconsistent with respect to sleep architecture and adenoidal size [140-145] (Tables e10).

Conclusions and recommendations
Intranasal steroids as a single intervention is not recommended for treatment of adult obstructive sleep apnea syndrome (C). Intranasal steroids is recommended for childhood obstructive sleep apnea syndrome in the presence of co-existing rhinitis and/or upper airway obstruction due to adenotonsillar hypertrophy (B).
1.7. Nasal Dilators

Rationale
The nasal vestibule is a major site of resistance to airflow in healthy subjects. A high nasal resistance may increase snoring. Activation of the alae nasi and alar retraction reduce resistance to airflow and improve ventilation. Nasal dilators might improve sleep and breathing by widening the nostrils. They are fitted to exert a dilating force on the nasal valves by means of its elasticity.

Search Strategy
Data bases individually searched: PubMed and Medline. Literature search using the terms obstructive sleep apnoea AND nasal dilator (no limits) was performed. Original studies published in English by April 2010 were included. In addition, the reference list of the included trials was evaluated. In total, 14 studies – two RCTs and 12 other clinical trials - could be identified, published between 1988 and 2005.

Overview of evidence
Nasal dilation increases nasal cross section by 14 to 25 % and is associated with a distinctive and sustained reduction in nasal resistance and the oral fraction of ventilation during sleep [146]. External nasal dilators are well tolerated [147]. They were able to reduce the maximum snoring intensity in one study [148], but in another study snoring was not influenced at all [149]. Sleep architecture remains almost unchanged in patients with habitual snoring [147, 149] and is improved slightly in patients with obstructive sleep apnoea[146]. OSA severity was reduced in one study with 10 patients with OSA and nasal obstruction [146], but not in another study with 30 patients with obstructive sleep apnoea [150], and in a study with 18 patients with upper airway resistance syndrome there was no additional effect on sleep-disordered breathing [151]. It is possible that there are parameters predicting the efficacy of the devices as hyperplasia or hypertrophy of the lower turbinates, septal deviation, and/or allergic rhinitis, no or only minor pharyngeal obstruction, or age less than 55 years [152] (Table e11).
Internal nasal dilation reduces nasal resistance by 31 to 65% [153, 154] and thereby improves the airflow [45]. Devices have a weak effect on snoring in patients without nasal pathology [155], even in populations with different external nose structures (Caucasians and Japanese) [156], and a substantial decrease in snoring noise in patients with habitual snoring and/or obstructive sleep apnoea [157]. The devices have only little or no effect on the number of apnoeas, hypopnoeas, oxygen saturation during sleep, or hypersomnolence during the day [154, 157, 158] (Table e12).

In summary, the published data do not support the hypothesis that nasal dilators are effective in reducing snoring, or in improving sleep-disordered breathing, or sleep architecture in obstructive sleep apnoea. Nasal dilators are not recommended for reducing snoring, or for improving sleep-disordered breathing, or sleep architecture in obstructive sleep apnoea (D).
2. Surgical therapy

2.0. Pathophysiological impact of nasal obstruction in the development of obstructive sleep apnoea

Breathing through the human nose appears to have an effect on both ventilation and upper airway muscle tone. In an experimental study, McNicholas and co-workers [159] previously demonstrated increased ventilation during nasal ventilation compared to mouth breathing. White et al [160] investigated the effects of local nasal anesthesia on ventilation during sleep in healthy men. The application of lidocaine resulted in a fourfold increase in the number of both central and obstructive apnoeas, suggesting a stimulating effect of nasal airflow on respiratory muscle activity and upper airway stability. The latter has been confirmed by Basner and co-workers [161], who demonstrated that nasal ventilation was associated with higher upper airway dilator muscle activity than breathing through the mouth in healthy volunteers. More recently, Kotsourelakis et al. [162] investigated the relationship between breathing route and apnoeic events in patients with OSA and controls. Patients with OSA had more frequent oral breathing epochs during sleep than controls. Oral breathing epochs furthermore correlated with respiratory disturbances during sleep.

It may be argued that nasal obstruction may predispose to sleep disordered breathing. In fact, a number of studies demonstrated an increased number of arousals, more frequent sleep stage changes, and/or an increase in the number of obstructive apnoeas and hypopnoeas during sleep associated with nasal occlusion under experimental nasal obstruction [163-165]. Similarly, there is evidence of sleep-related breathing disorders associated with nasal obstruction as a result of bilateral nasal packing after nasal surgery [166-169]. One potential limitation in these reports may be the potential influence of general anesthesia on the prevalence of postoperative upper airway obstruction. In a recent report, however, Armengot and co-workers [170] demonstrated equivalent episodes of nocturnal hypoxemia both in patients who had nasal packing postoperative nasal surgery and in those who had nasal packs for epistaxis but did not receive surgery.

In summary, there is evidence of a protective effect of nasal breathing on upper airway stability. The current literature furthermore suggests that patients with OSA are more likely to breath through the high resistance pathway of the mouth and
thereby promoting more negative intraluminal pressure in the pharynx, predisposing to pharyngeal occlusion and, thus obstructive sleep apnoea events. Moreover, there is evidence on both inducing and worsening of sleep disordered breathing due to nasal occlusion.

2.0.1. Effects of nasal surgery on obstructive sleep apnoea

Rationale
Due to the impact of nasal obstruction, improved nasal patency is expected to alleviate sleep disordered breathing. Furthermore, there is an expected relationship between nasal airway obstruction and CPAP tolerance, providing a physiological basis for improved CPAP compliance after nasal surgery [171]. Accordingly, the aim of this review is to assess the efficacy of nasal surgery on sleep apnoea severity, sleep quality, and symptoms in adults with diagnosed OSA.

Search criteria
The authors performed searches in Pubmed and Medline. In addition, the authors underwent a manual search of the reference section of each cited article. Keyword combinations: OSA and nasal obstruction, OSA and nasal surgery, sleep apnoea and nasal surgery, sleep apnoea and nasal obstruction, sleep apnoea and nose, nasal ventilation and OSA. Studies with snorers only or those with sleep breathing disorders other than OSA, and studies in which nasal surgery was associated with other surgical procedures in the treated subject (i.e., adenotonsillectomy or others) were excluded.

Overview of the evidence
14 reports with adult patients suffering from mild to severe sleep disordered breathing and nasal obstruction have been published either as case-series or retrospective analyses, and one report [172] was conducted as a prospective, randomised, sham-controlled trial (Tables e13) [172-183]. The most frequently observed pathologic finding in the preoperative ENT examination was nasal obstruction due to deviated nasal septum. Accordingly, septal surgery (submucosal resection with or without turbinectomy) was the most frequently applied surgical technique in these reports. All the studies (n=5) that have performed rhinomanometry
reported significant postoperative improvements in total nasal resistance, indicating postoperative improvements in nasal airway patency in the patients.

Only two studies [180, 181] reported significant improvements of the respiratory disturbances. One study [177] reported a significant improvement in AHI and sleep architecture in those with normal preoperative cephalometric measurements, but no beneficial effect in a group of patients with abnormal cephalometric measurements. There have been improvements in either sleepiness scales or daytime energy levels in six reports, and a reduction in therapeutic CPAP pressure required to alleviate OSA in two studies.

Conclusions and recommendations
Nasal surgery as a single intervention is not recommended for treatment of obstructive sleep apnoea syndrome (C). Nasal surgery is recommended for reducing high therapeutic CPAP pressure due to nasal obstruction (C).

2.1.1. Tonsillectomy and tonsillotomy
Rationale
The main upper airway anatomical alterations correlating with OSA include an enlarged tongue, soft thick palate, web posteriorised in relation to the oropharynx, long and thick uvula, and/or hypertrophic tonsils. Of note, those studies attempting to correlate the presence of anatomical alterations with disease severity found the highest correlations for tonsillar hypertrophy [184, 185]. While substantial bilateral tonsillar hypertrophy in adults is rather rare, adenotonsillar hypertrophy is the most common etiology of OSA in children. The aim of this literature search was to assess the efficacy of surgical tonsillectomy on sleep apnoea severity, sleep quality, and symptoms in adults with OSA and tonsillar hypertrophy.

Search criteria
Data bases individually searched: PubMed and Medline. Keyword combinations: Tonsillectomy and obstructive sleep apnoea, tonsillotomy and obstructive sleep apnoea, tonsils and sleep, tonsillar hypertrophy and sleep apnoea, adenotonsillectomy and sleep apnoea. Studies with tonsillectomy by means of radiofrequency ablation, studies with tonsillectomy as part of UPPP or multi-level
surgery, reports on surgical outcomes of the upper airways without explicit information on sleep results in relation to tonsillectomy were excluded.

**Overview of the evidence in adults**

All reports have been published either as case-series or retrospective analyses (Table e14). Common to most of the reports is the lack of quality of life measures, the absence of a control group, and the lack of reporting surgical complication rates. More recent studies, however, reported consistent and significant improvements in the AHI after tonsillectomy. Despite significant improvements in respiratory parameters, there was evidence of residual sleep disordered breathing in most reports. More recent trials by Martinho et al. [186] and Nakata et al. [187] investigated patients with OSA who where either intolerant to a CPAP trial or required high CPAP pressures to treat upper airway obstruction due to tonsillar hypertrophy. Based on these reports tonsillectomy may have a similar role as nasal surgery in increasing the use of CPAP in patients with tonsillar hypertrophy, or when CPAP therapy is not possible as the first choice of therapy.

**Overview of the evidence in children**

Thirty eight “particular case-control studies” (n = 10, Evidence level 3b), case-control studies of limited quality (n = 2, level 4), and case-series without controls (n = 26, level 4) investigating patients between 1 and 20 yrs of age who underwent (adeno-) tonsillectomy were included in the analysis (Table e15). Common to most reports is that the indication for surgery was based on evidence of upper airway obstruction, either by means of clinical signs or symptoms and/or poly(somno)graphically diagnosed sleep disordered breathing. Most studies investigated the effects of tonsillectomy as a combined procedure with adenoidectomy. The study population was very heterogeneous, including children who underwent tonsillectomy because of snoring, suspected obstructive sleep apnoea, poly(somno)graphically verified sleep apnoea (using an Al >1 or AHI > 5/hr as a diagnostic cut-off), recurrent tonsillitis, and/or symptoms of upper airway obstruction without further explanation. Follow-up studies were performed between a few days postoperatively and up to 12 months after surgery.

All studies showed significant postoperative improvements in respiratory parameters.
Furthermore, there is some evidence of improved sleep architecture and improved quality of life scores, OSA symptom scores, and/or child behavioural scores. The literature also provides evidence for beneficial treatment effects beyond the reported outcomes on sleep parameters and quality of life scores, such as rapid increase in growth rate [188], improvement in Insulin like growth factor-I levels [189], improvements in systemic inflammation, lipid profiles, and endothelial function [190]. Notably, most of the studies that investigated children with moderate to severe OSA observed persistent sleep disordered breathing in a clinically relevant proportion of children. Complete resolution of OSA was reported as low as 25% [191]. This raises important issues regarding the efficacy of adenotonsillectomy as the only intervention for OSA in children. Accordingly, repeated sleep testing has been recommended particularly in those with persisting symptoms of upper airway obstruction (such as snoring) and/or in those with severely abnormal preoperative PSG results [192].

Conclusions and recommendations
Tonsillectomy as a single intervention is recommended for treatment of adult obstructive sleep apnoea in the presence of tonsillar hypertrophy (C). Adenotonsillectomy is recommended for treatment of childhood obstructive sleep apnoea in the presence of adenotonsillar hypertrophy (C).

2.1.2. Radiofrequency surgery of the tonsils
Rationale
New techniques of tonsillectomy or tonsil volume reduction (tonsillotomy) are developed in order to reduce postoperative pain and bleeding rates. Temperature-controlled radiofrequency tonsil reduction is performed by introducing a probe is introduced into the tonsil and heated to temperatures ranging from 40°C to 70°C. A plasma field consisting of highly ionised particles is formed at the probe’s surface that breaks down the molecular bonds of local tissue, with a reduction in heat dissipation to surrounding structures. The key innovation of radiofrequency tonsil reduction is the concept of subtotal intracapsular tonsil reduction that avoids injury to the pharyngeal constrictor muscles.
Search criteria
Data bases individually searched: PubMed and Medline. Keywords: Radiofrequency tonsillotomy and radiofrequency tonsil surgery for sleep apnoea. Articles dealing with pediatric samples, multilevel surgery, infectious tonsillar disease reviews, meta-analysis, case-reports and guidelines were excluded.

Overview of the evidence
Four studies matching the inclusion criteria of this paper were found (Table e16, e17). No polysomnographic data were available in these studies.

Nelson [193] showed that performing radiofrequency ablation of the tonsils with the use of a 2-needle probe does not damage the underlying pharyngeal muscle in vitro. A reduction of 70.8% in tonsil size was achieved in an in vivo study (N=9) without post-operative bleeding. Moderate to severe post-operative pain on day 1 was present in 4 out of 9 patients but disappeared over a week. An important improvement in subjective outcome, speech comfort, swallowing and throat irritation was reported. The same group confirmed these findings in a 12 months follow-up study [194] in 12 patients with obstructive tonsil hypertrophy. Friedman et al [195] reported a reduction of 53.6% in tonsil size after 12 weeks. The amount of tonsil reduction had a wide range and was unpredictable. Only mild post-operative pain was observed in all patients. No intra- or postoperative bleeding was noticed. However, radiofrequency tonsil reduction was not recommended as a standard technique for tonsil reduction. Ericsson et al. compared efficacy and side effects of tonsillotomy (N=31) and tonsillectomy (N=43) [196] in patients with recurrent tonsillitis or obstructive hypertrophy. The tonsillotomy group had less intra operative bleeding and no postoperative bleeding, while the tonsillectomy group had 6 postoperative bleedings. Postoperative pain was significantly less in the tonsillotomy group. In a follow-up study 1 year after radiofrequency tonsillotomy, Ericsson et al. showed that both tonsillotomy and tonsillectomy equally effectively improved quality of life.

Conclusions and recommendations
Radiofrequency tonsil reduction appears to be a minimally invasive procedure with limited morbidity compared with tonsillectomy. The amount of tonsil reduction is significant but unpredictable. No conclusion on efficacy in obstructive sleep apnoea
Radiofrequency tonsil reduction appears to have fewer side effects such as intra- and postoperative bleeding and less postoperative pain. Tonsil regrowth might occur but has not been studied thoroughly. Radiofrequency tonsil reduction is not recommended as a single procedure for the treatment of obstructive sleep apnoea (D).

2.2.1. Uvulopalatopharyngoplasty (UPPP)

Rationale
Uvulopalatopharyngoplasty (UPPP) and laser-assisted uvulopalatoplasty (LAUP) aim to diminish anatomical upper airway obstruction at the oropharyngeal level by reducing soft palate redundancy [197]. UPPP enlarges the retro-palatal airway by trimming and reorienting the posterior and anterior lateral pharyngeal pillars, and by excising the uvula and the posterior soft palate [197]. LAUP is an office-based surgical procedure that progressively shortens and tightens the uvula and palate through a series of carbon dioxide laser incisions and vaporizations [197]. In the large majority of apneic patients, upper airway collapses occur at multiple levels i.e. both at the retropalatal level and behind the tongue base. Therefore, a surgical success with UPPP or LAUP can only be anticipated when pharyngeal collapse is limited to the retropalatal area which is rarely the case in obese or severe sleep apnoea [198]. For these reasons surgical procedures dedicated to soft palate have been essentially studied in selected mild to moderate OSA populations with predominant oropharyngeal narrowing.

Search criteria
Data bases individually searched: PubMed and Medline. Keyword combinations: Sleep apnea AND uvulopalatopharyngoplasty. Sleep apnoea AND LAUP or laser assisted uvulopalatoplasty. Limit: Clinical Trial; no other limitations. Only prospective studies were taken into account.

Uvulopalatopharyngoplasty
Overview of the evidence
Randomised clinical trials (RCT) comparing UPPP to no treatment or sham surgery groups are lacking. Different definitions of clinical success are proposed, the most
common that we will use in this review is a more than 50% reduction in AHI with a post-surgery AHI<20/hour of sleep. The number of patients assessed is generally limited with only few publications evaluating UPPP alone without adjunctive surgical procedure. Even prospective studies demonstrate nearly systematic inclusion biases. At the end, the majority of the available papers are clinical case series ranked as level 4 evidence. Interpretation of the “UPPP studies” is even more complex owing to the existence of many surgical techniques dedicated to the soft palate [199].

Overall, UPPP has a reported success rate of approximately 50% in unselected populations of mild to moderate sleep apnoea [197, 198]. In prospective studies (table e18) the mean success rate (50% reduction in AHI, an AHI of ≤ 20, or both) ranged from 30 to 78%. Such differences from one study to another are probably reflecting selection biases with potential good candidates being previously selected [200]. These studies also mainly included young or middle age and lean subjects with mild to moderate sleep apnoea.

Failure of UPPP is usually attributed to secondary sites of obstruction located more caudally in the upper airway or to persistent retropalatal collapse due to an increased thickness of the soft palate after the procedure [199, 201]. The percentage of patients attaining UPPP success was 52% in case of isolated oropharyngeal obstruction compared to 5% in situations of associated retrolingual narrowing [202]. However, selecting appropriate patients for UPPP surgery remains challenging [200] as physical examination, imaging techniques, upper airway pressure measurements and endoscopic examination are not systematically used and no evidence exists demonstrating that any criteria are sufficiently useful in predicting good surgical outcomes. Friedman et al. [203] developed an anatomic staging system based on tongue-palate position, tonsil size, and BMI to classify patients. In a case series changes in AHI were significantly correlated with Friedman tongue position (FTP) and tonsil size [200]. Patients with retrolingual collapse or narrowing demonstrated by clinical criteria or by techniques evaluating upper airway size and/or function, should not be proposed to UPPP surgery.

In the few studies having examined long term evolution after surgery, efficacy of UPPP seems to diminish over time [88]. This seems to justify a long term follow-up of
these patients. UPPP is substantially less effective as compared to oral appliances [88, 204].

Other outcomes such as subjective [205, 206] or objective sleepiness, sleep structure and fragmentation, quality of life [207] or cardiovascular changes have been rarely reported. However, improvement of the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS) [206], low grade inflammation [208], and endothelial function [209] have been described.

Serious life-threatening complications including intubation difficulties, bleedings and acute upper airway obstruction have been observed after UPPP with a 1.5% incidence and a mortality rate of 0.2% in a large prospective study including 3,130 patients [210]. Long-term side-effects (e.g. swallowing, globus sensation, voice changes, nasopharyngeal stenosis) persisted after UPPP in 58% of the patients [211]. Finally, having undergone UPPP has been proposed as a risk factor for CPAP non-compliance [212]. Leaks and mouth dryness are increased when using CPAP in patients with prior UPPP and may impair CPAP tolerance.

Conclusions and recommendations
UPPP is a single-level surgical procedure working only in selected patients with obstruction limited to the oropharyngeal area. UPPP cannot be recommended except in carefully selected patients (C). When proposing UPPP, potential benefits should be weighed against the risk of frequent long-term side effects among them velopharyngeal insufficiency, dry throat, and abnormal swallowing are the most common. Analysed studies were prospective but with selection biases, and therefore do not provide high-level evidence (C).
2.2.2. Laser assisted uvuloplasty (LAUP)

Overview of the evidence

Data bases individually searched: PubMed and Medline. Two randomised controlled trials are available [213, 214]. Ferguson et al. compared LAUP to conservative treatment in 46 mild OSA patients with a mean follow-up of 7 months. There was a statistically significant but not clinically relevant 21% reduction in AHI after LAUP (from 19 to 15/h) No improvement was found for subjective sleepiness and quality of life [213]. Surgery reduced snoring intensity and frequency. Larrosa et al. failed to find a difference between LAUP and a Sham surgery [214] in sleepiness, quality of life or respiratory disturbances. After LAUP surgery, airway is further compromised by edema in the early postoperative period with a potential risk of OSA exacerbation (Table e19).

Conclusion and Recommendation

In mild OSA, laser assisted uvulopalatoplasty has not demonstrated any significant effect neither on OSA severity nor in symptoms or quality of life domains and is therefore not recommended. (B).
2.2.3 Radiofrequency surgery of the soft palate

Rationale

The term “radiofrequency surgery” in the context of palatal interventions is usually focusing on the interstitial electrosurgical treatment with stiffening of the tissue. Furthermore, cutting devices based on radiofrequency energy have also been developed to excise palatal tissue (radiofrequency assisted uvulopalatoplasty: RAUP) [215-217]. Finally, various combinations have been proposed, for example the combination of interstitial radiofrequency surgery and RAUP (RF-UPP)[218]. Tissue excision is usually performed as a single step procedure, whereas the interstitial application routinely requires repeated treatment session.

Search criteria

Data bases individually searched: PubMed and Medline. Keyword combinations: “radiofrequency”, “palate” and “sleep apnea”. Only studies using radiofrequency surgery as an isolated approach were analyzed. Studies with patients with primary snoring were only selected with regard to morbidity and complications. In addition, a recent review was evaluated regarding potential additional publications [219]. Studies were excluded if they either did not provide sufficient objective outcome measures [220-222] or the baseline AHI was <5 [223] or 10 [220, 224, 225] and the primary intention was to treat snoring.

Overview of the evidence

The data concerning obstructive sleep apnea is limited and can hardly be compared due to the differences in devices and surgical techniques.

Improvements in respiratory parameters have been described in groups of mild to moderate and more severely affected patients under interstitial radiofrequency at the soft palate [226, 227]. Moreover, radiofrequency assisted uvulopalatoplasty has been shown to be superior to interstitial radiofrequency surgery, but was associated with higher postoperative morbidity [217]. However, there are inconsistent findings in daytime sleepiness or other sleep parameters. A most recent, placebo-controlled study has shown that a single step RF-intervention at the soft palate is not effective to treat obstructive sleep apnea (table e20) [228].
No serious adverse events after interstitial radiofrequency have been reported, though overall complication rates ranged from 0% to 50% [229-233]. The most frequently reported complication was mucosal erosion/ulceration. A small number of studies reported moderate complications in terms of severe palatal damage (palatal fistula, uvula loss/sloughing) [229, 230, 234, 235]. Postoperative pain was minimal in nearly all published papers [236-239]. No significant impact on fundamental frequency and formant frequency of vowels was detected. Postoperative morbidity of radiofrequency tissue resection or combined approaches appears higher [217, 218]. Nevertheless, postoperative pain after RAUP is still significantly less pronounced and postoperative morbidity is still significantly lower compared to LAUP [216].

Conclusions and recommendations
No controlled trials are available in sleep apnea. All case series demonstrate a significant reduction in AHI after radiofrequency surgery. Radiofrequency surgery cannot be recommended except in carefully selected patients (C).
### 2.2.4.1. Uvulopalatal flap

**Background**

The uvulopalatal flap has been introduced as a modification of the classic uvulopalatopharyngoplasty (UPPP) [240]. By the removal of the oral mucosa and salivatory glands and incisions bilaterally into the posterior pillar an uvulopalatal flap is created. This flap is rotated upwards and sutured into the defect. The main disadvantage compared to UPPP is that despite preservation of all muscles no visible uvula is left acting as lumbricating structure for the palate.

**Search criteria**

Data bases individually searched: PubMed and Medline. Keyword combinations: “uvulopalato or uvulopalatal and apnoea” and Boolean logic. 26 articles were further analysed. 13 articles were excluded (language, reviews, expert opinions, not related with sleep disordered breathing).

**Overview of the evidence**

The evidence levels of the studies identified vary between 3b and 4. The data`s evidence is restricted by the fact that the 12 studies are published by only 3 working groups. Therefore, it seems possible that several subjects might be included in multiple publications.

The procedure can be performed under local and general anesthesia [241-243]. Complaints and complications are similar to a gentle UPPP [240]. Transient nasal regurgitation has been reported in 4% of the cases [241]. Permanent velopharyngeal incompetence or nasopharyngeal stenoses have not been reported so far. All working groups (6/12 studies) combined the uvulopalatal flap with other surgeries of the nose and/or the tongue base [240]. Powell et al. compared classic UPPP with the uvulopalatal flap in a group of 80 patients undergoing multi-level surgery (level of evidence 3b). The tongue base procedures were identical in both study groups. Both, UPPP and the flap showed comparable results with regard to effectiveness for OSA, amount of tissue removed and complications. Six papers investigated the effect of an isolated uvulopalatal flap without any other surgeries at the same time [241, 244-248]. The AHI decreased significantly from 45 to 14 after six to twelve months after
surgery. Surgical success (defined as 50% reduction in AHI and reduction of AHI below 20) was calculated as 81.5%. Significant improvement of quality of life as measured with the Mental Health 5 questionnaire [245]. SF-36, Epworth Sleepiness Scale and Snore Outcome Survey (SOS) were reported compared to baseline. All series were done by the same working group (Table e21, e22).

Conclusions and recommendations
Studies investigating the uvulopalatal flap with tonsillectomy for OSA show a significant improvement of the severity of OSA and quality of life. No controlled studies exist comparing the uvulopalatal flap to other treatment modalities for OSA. The levels of evidence of all studies were classified as 4 (C). So far, no cut-off points concerning BMI an AHI were identified limiting the use of the uvulopalatal flap. Therefore, it has to be kept in mind that surgical success rates decrease with increasing BMI and AHI in general. Various study groups (3b) found, that the uvulopalatal flap may be combined with other surgeries of the nose and the tongue base in the sense of multi-level surgery with acceptable perioperative risk. The uvulopalatal flap turned out to be as effective as UPPP (3b).

Due to a lack of evidence uvulopalatal flaps are not recommended to treat simple snoring. Uvulopalatal flaps can be recommended for OSA in patients with palatal obstruction (C). Uvulopalatal flaps are a safe procedure that can be combined with other types of surgery within the upper airway to address OSA (B).
2.2.4.2. Pillar method

Rationale
The Pillar method consists of placing three cylindrical, non-resorbable polyethylenterephthalat (PET) implants (18 mm long) into and parallel to the midline of the soft palate with a distance of 3 mm to each other. The implants themselves as well as the surrounding fibrosis are intended to reduce three-dimensional flutter of the soft palate and therefore inspiratory airway resistance [249].

Search criteria
Data bases individually searched: PubMed and Medline. Keyword combinations: “palate”, “implant” and “sleep apnoea”. Only prospective studies were included. For the analysis of clinical outcome, only studies using the Pillar® technique as an isolated approach were analysed. Studies concerning snorers were only selected with regard to morbidity and complications. There is no experience in children so far.

Overview of the evidence
There are six case series and two randomised, placebo-controlled, double-blind trials (table e23). Placebo treatment consisted of inserting an empty delivery tool (no implant preloaded). Most studies included only patients with an AHI between 10 and 30, BMI <32 kg/m², no or small palatine tonsils, and no sign of retrolingual collapse. Only Friedman included more obese patients (BMI<40 kg/m²). The six case series showed a reduction of the AHI >50% and postoperative AHI <10 in 15-50% of the cases 3-15 months after the procedure [250-254]. Both randomised, placebo-controlled, double-blind studies show a superiority of implants over placebo. However, results are conflicting, as Steward et al. found a non-significant increase of AHI [255], in contrast to Friedman et al., who reported a pronounced reduction of AHI [250]. The ESS showed significant improvement in all case series and in the level 1b study conducted by Friedman. No difference was found compared to the placebo group in the study of Steward. Functional parameters as assessed by questionnaires such as the SF-36 [250] and the FOSQ [255] demonstrated a significantly greater improvement in the treatment group compared to placebo.
Only minor discomfort such as minor sore throat or foreign body sensation was reported within the first four days post-procedure. Infections, mucosal irritations or ulcerations at the implant entrance site were reported in less than 1% of the patients. Pain could be managed with simple analgesics such as paracetamol. There was no significant speech or swallowing disturbance after the procedure [256-260]. A partial extrusion happened in 10.3% of the patients or 4.1% of the implants in average.

Conclusions and recommendations
Pillar® implants as an isolated procedure are superior to placebo and the respiratory results remain stable over the first 15 postoperative months but the overall success rate is limited. Therefore pillar implants cannot be recommended and may only be considered in patients with mild to moderate OSA, who are suitable with regard to their overall physical condition (not or only moderately obese, no or small tonsils, no sign of retrolingual obstruction), if conservative approaches are not accepted by the patient.(B).
2.3. Tongue base and hypopharynx

2.3.1. Radiofrequency surgery of the tongue base

Rationale
Interstitial radiofrequency surgery of the tongue base was first investigated in a porcine model using a temperature-controlled radiofrequency device. The procedure turned out to be safe and was transferred to the use in patients suffering from obstructive sleep apnoea. Various different devices are available, although the majority of the published trials have used temperature-controlled RF surgery.

Search criteria
A literature search was performed in PubMed (U.S. National Library of Medicine). Keyword combinations: “radiofrequency”, “tongue” and “sleep apnoea”. In addition, a recent review was evaluated regarding potential additional publications. For the analysis of clinical outcome, only studies using interstitial, transoral radiofrequency surgery as an isolated approach were analysed. Studies using combined approaches in terms of multilevel surgery were only selected with regard to morbidity and complications. Data regarding a transcervical radiofrequency approach were excluded. One study was excluded due to the high number of dropouts and the inhomogeneous mixed patient sample (snoring and obstructive sleep apnoea).

Overview of the evidence
In general, despite one comparative trial [261] only non-controlled case series have been published. All studies have shown a statistically significant reduction in daytime sleepiness and all but two demonstrated a statistically significant reduction in AHI, although the overall effect seems limited (table e24) [262, 263]. Most trials presented follow-up periods between 1 and 4 months. The longer term follow-up study (28 months) showed an increase in AHI indicating a relapse of OSA [264]. In contrast, Steward et al. have documented the stability of the results at least over a median follow up of 23 months [265]. A series of non-controlled trials has been published regarding combined radiofrequency surgery at the tongue base and the soft palate [266, 267]. However, Woodson et al. compared multilevel radiofrequency surgery at the tongue base and the soft palate with CPAP and placebo (sham-CPAP) [261]. Although the AHI did not improve in the radiofrequency group, subjective and
functional outcome measures improved statistically significantly. Postoperative pain appears to be comparable to UPPP with tonsillectomy [263]. The postoperative complication rate varies between 0 and 41%, mostly below 5% [229, 232, 233, 263, 267-270]. A severe potential complication is the formation of an abscess of the tongue base[229, 232, 262, 271]. No changes of swallowing or speech were observed [232, 263, 267, 271]. The addition of radiofrequency surgery to other surgical approaches such as UPPP, nasal surgery, tonsillar surgery, palatal implants or hyoid suspension did not lead to an increase in morbidity [270, 272-277].

Conclusions and recommendations
The majority of the studies demonstrated a statistically significant, but limited reduction in AHI and daytime sleepiness, although the data were based on non-controlled case series with short follow up periods (level of evidence: 3b). Therefore radiofrequency surgery of the tongue cannot generally be recommended as an isolated or combined procedure and may only be considered in selected patients with mild to moderate sleep apnea intolerant to conservative treatment as long as the overall condition appears suitable (non- or only moderately obese patients with retrolingual obstruction) (C).
2.3.2. Hyoid suspension

Rationale
Hyoid suspension aims at avoiding the back positioning of the tongue during sleep. Meanwhile, most surgeons favour the suspension of the hyoid to the thyroid cartilage with and without myotomies of the supra- and infrahyoid muscles.

Search criteria
Data bases individually searched: PubMed and Medline. Keyword combinations: “hyoid suspension and apnoea” and Boolean logic. Variations of the catchwords were admitted. The remaining 21 articles were included in the analysis (table e25).

Overview of the evidence
The evidence levels of the studies identified vary between 3b and 4. The perioperative risk of surgery is generally increased in OSA. In addition, temporary dysphagia up to 4 weeks, self-limited aspiration within the postoperative period, hematomas, seromas, disturbance of wound healing, as well as temporary articulation distortions have been reported. Most authors use the hyoid suspension as a part of multi-level surgery for severe OSA secondarily after CPAP failure (table e25). Only 3 short-term studies investigated the effect of an isolated hyoid suspension for OSA [278-280]. The AHI decreased significantly from 36 to 21 after the hyoid suspension (table e26). The ESS score fell statistically significantly from 8 at baseline to 5 after surgery [278, 280]. Two studies [281, 282] compared multi-level surgery with and without hyoid suspension. The concept including hyoid suspension was significantly more effective as compared to the control group.

Conclusions and recommendations
The published data have to be regarded as preliminary. Randomised studies comparing the hyoid suspension with CPAP do not exist. The hyoid suspension is an invasive surgical technique although the complication rate is moderate. Therefore, hyoid suspension may be combined with other procedures in multi-level surgery. The method may be considered in CPAP failure. Surgical success rates decrease with increasing BMI and AHI (C).
Due to a lack of evidence hyoid suspension is not recommended for simple snoring. Hyoid suspension as an isolated procedure can be recommended for OSA in patients with retrolingual/hypopharyngeal obstruction (C). Hyoid suspension is a safe procedure that can be combined with other types of surgery within the upper airway (B). Hyoid suspension as a part of a multi-level surgery concept can be recommended for OSA in patients with combined retropalatal and retrolingual/hypopharyngeal obstruction (B).
2.3.3. Tongue base and hypopharynx: partial tongue base resection and other treatments

Search criteria
Keyword combination: tongue base surgery for sleep apnoea and hypopharyngeal surgery for sleep apnoea. Inclusion: Studies where tongue base resection or tongue suspension were part of a multi-level approach are included. Medline search: tongue base surgery for sleep apnoea and hypopharyngeal surgery for sleep apnoea up to 1/1/2009. Reference lists of all identified articles were searched for additional studies.

Overview of the evidence

- Laser Midline glossectomy (LMG) (Table e27).
  It has been hypothesized that a midline portion of the tongue base and removal of excessive tissue such as redundant lingual tonsils would enlarge the hypopharyngeal airway [283]. The intervention carries an inherent risk for significant postoperative pharyngolaryngeal edema and requires a temporary tracheotomy. Fujita and Mickelson included patients with severe persistent OSAS after UPPP and selection was based upon clinical examination and fiberoptic laryngoscopy with Mueller manoeuvre [283, 284]. Side effects were considered minor and no persistent voice changes or dysphagia were reported. Andsberg and Jessen [285] found a 50% reduction in apnoea index in 56% of the subjects after eight-years follow-up. Of note, 23% complained of postoperative complications 98 months postoperatively.

- Other approaches for tongue base reduction (plasty – resection) (Table e28)
  - Tongue base reduction with hyoepiglottoplasty (TRBHE)
    Chabolle et al. and Sorrenti et al. performed a subtotal tongue base reduction through a cervical approach preceeded by lingual neurovascular bundle identification and derouting, epiglottal verticalisation, mouth floor horizontalisation, and hyoid bone repositioning termed tongue base reduction with hyoepiglottoplasty (TBRHE) [286, 287], mostly combined with UPPP. A 100 % success rate was achieved at 6 months follow-up in severe OSA patients with severe macroglossia and hyolingual
abnormalities in the absence of craniofacial deficiencies [287]. 3 of 10 patients had swallowing abnormalities 6 to 19 months postoperative but all were able to resume a normal diet. The most relevant complication was a submental abscess which was attributed to the use of non-absorbable sutures.

- **Lingualplasty (LP)**
  Woodson and Fujita modified the technique of LMG to include lingualplasty in which tongue excision is extended more posterior and lateral [288]. Candidates for LP were those with CPAP intolerance and UA collapse caused by large lingual tonsils or tongue base, rather than lateral wall collapse. LP requires preoperative tracheotomy and in their original paper, removal of additional lingual tonsils or redundant tissue of the epiglottis or arytenoids was included. In their series of 22 patients, 8 had combined LP and UPPP, the remaining had LP alone. There was a significant perioperative complication rate (27%), but no long-term complications and the authors concluded that LP was more effective than LMG alone.

- **Lingual tonsillectomy (LT)**
  During LMG, the central part of the tongue is resected. Theoretically, this technique might have limited efficacy in selected patients with swollen lingual tonsils. Li et al. compared the efficacy of combined treatment by extended uvulopalatal flap (EUPF) with either midline glossectomy or lingual tonsillectomy in a series of 12 consecutive non-obese OSA patients [289]. They found that EUPF+LMG was highly effective in treating OSA in selected patients with type 2 obstruction (83% of success), whereas EUPF+LT was found to have no effect on OSA.

- **Palatopharyngoglossoplasty (PPGP)**
  Djupesland et al. developed a modified surgical technique based upon a combination of uvulopalatopharyngoplasty and removal of redundant tissue at the lateral aspects of the tongue base [290]. AHI decreased from 54/h (range 10-98) to 31 (range 0-61) in 20 OSA patients 8.7 months after PPGP [291]. The AHI improved > 50% in 50% of the patients (n=10).
• **Uvulopalatopharyngoglossoplasty (UPPGP)**

This technique combines UPPP with a bilateral resection of redundant soft tissue at the lateral aspects of the tongue base [292]. Screening oximetry and ambulatory polysomnography were repeated. The response rate in 19 OSA patients 6 to 12 months after surgery was 67% and no major complications were encountered.

• **Glossopexia**

The glossopexia consists of a combination of a tongue resection plasty and an anterior suspension of the tongue using strips of fascia lata [293]. All of 8 patients with persistent OSA after UPPP were tracheotomised and had subjective improvement, but reliable improvement documented by PSG after 12-24 months was obtained in only 2 patients. In addition, postoperative cephalometry did not reveal a change in the vertical or horizontal position of the hyoid bone or in the dimensions of the posterior airway space but relevant side effects such as decreased sensitivity of the chin and tongue, immobility of the tongue, decreased sense of taste and slight difficulties of articulation, persistent oedema of the tongue, rejection of the fascia lata and serious infection of the tracheotomy spreading to the mediastium had to be reported. Therefore, this technique has no role in the surgical management of OSA.

The role of these modified techniques of glossopexia, PPGP and UPPGP and LT in the surgical treatment of OSA is unclear as no later reports on these techniques have been published so far.

• **Tongue base suspension (Table e29)**

The Repose® system (InfluENT Inc®) is a minimally invasive surgical kit that uses a titanium screw and permanent suture to anchor/stabilise the tongue base to the inner mandibular cortex. Tightening of the suture provides support to the anterior hypopharyngeal airway and tongue base, thus preventing collapse at the retrolingual level. According to DeRowe and Woodson [294], the aim is not to permanently move the tongue forward, but rather to stabilise the tongue base level by adding rigidity of the scar tissue encased suture anchored anteriorly. The treatment is reversible as the suture can be removed. Patient selection was based upon fiberoptic examination and Mueller manoeuvre. The incidence of postoperative complications ranged from 15 to 33% including infections with floor of mouth sialadenitis, dysphagia,
odynophagia, development of floor of mouth cyst or haematoma. Thomas et al. performed a randomised controlled trial comparing tongue advancement (mandibular osteotomy) with tongue suspension (Repose®) [295]. All patients underwent a simultaneous UPPP. There was no significant difference between both procedures in terms of response, postoperative pain, speech impairment or swallowing difficulties.

As the aim of the tongue suspension is to stabilise and support the tongue base, rather than to advance it, it is not surprising that Miller et al. and Terris et al. failed to find relevant changes in the posterior airway space [296, 297]. A significant improvement in airway collapse at the palatal and tongue base level was demonstrated when Repose® was combined with UPPP [295, 297].

Patients with moderate to severe OSA have UA collapse at multiple levels of the upper airway involving the retropalatal, retroglossal region and varying contributions from the lateral pharyngeal walls. Therefore, some authors proposed a combined retropalatal/retroglossal approach by simultaneously performing a UPPP and a tongue suspension procedure (Repose®) [296, 298-300]. It is hard to delineate the relative contribution of each single procedure to the final outcome [299, 301]. Sorrenti et al. suggested a limited role for tongue suspension in the surgical treatment of OSA as the results were inferior to those reported with genioglossus advancement and hyoid suspension in the treatment of retrolingual collapse. A second issue raised by these authors is the high cost of the Repose® kit and the probable poor stability of the suture over time [298].

**Summary**

Most studies on soft tissue tongue base surgery, excluding radiofrequency, were performed in subjects with severe OSA and concomitant obesity. In some reports, patients had already undergone UA surgery and were considered UPPP failures, others included patients who refused CPAP treatment. This selection bias is likely to affect the subjective appreciation of the results by the patients, which is mostly in contrast with the objective polysomnographic findings. The reviewed studies reported on significant improvements in snoring and daytime sleepiness. An improvement in the Functional Outcomes of Sleep Questionnaire score was reported in the study by Woodson et al. on tongue suspension [302].
Those studies that are limited to the use of one particular surgical technique have limitations in terms of number of patients included, design and time of follow-up. For those with a multilevel approach it is difficult to definitively define the efficacy of each procedure in terms of its contribution to a potential surgical cure.

**Conclusions and recommendations**

From the present data, it can be concluded that tongue base soft tissue procedures such partial resection of the tonguebase and tongue suspension (Repose®) cannot be recommended as a single treatment option for obese patients with moderate to severe OSA. The additional value of these techniques lies in the limited morbidity, the lack of cosmetic changes and the possibility to combine them with other procedures in a multilevel approach. There are at present no data to support their role in patients with mild disease (C).
2.4.1. Genioglossus advancement

Rationale
Genioglossus contraction enlarges both the velo- and the oropharynx and lowers the critical pressure without affecting the stiffness [116]. Nevertheless genioglossus is only one of many muscles that act in concert to prevent flow limitation in the pharynx. Genioglossus advancement (GA) aims to enlarge hypopharyngeal air space bringing forward the base of tongue.

Search criteria
Data bases individually searched: PubMed and Medline. Keyword combinations: Genioglossus advancement, genioplasty and sleep, genioplasty and obstructive sleep apnoea, hypopharyngeal surgery and sleep, hypopharyngeal surgery and obstructive sleep apnoea, tongue surgery and obstructive sleep apnoea.

Overview of the evidence
Genioglossus advancement consists in an advancement of the genial tubercle and genioglossus muscle. A sliding genioplasty can be performed with a complete manipulation of the chin position that is moved forward with a portion of the inferior mandibular border and attached muscles. The second technique consists in a geniotomy with a rectangular bicortical osteotomy centered over the genial tubercle. Recently, a minimally invasive procedure has been developed (the Repose® system) which try to reproduce the same effect with a tongue-base suture suspension.

No study investigates the effect of isolated genioglossus advancement for OSA. In multilevel surgery, when genioglossus advancement is the only hypopharyngeal procedure associated with velar surgery, GA demonstrated an improvement of postoperative AHI (Table e30) with a success rate of 60% [303, 304] in 5 series including 117 patients. The earliest studies realised between 1999 and 2004 in patients with severe obstructive sleep apnoea syndrome demonstrated the best efficacy of GA on AHI.

Conclusions and recommendations
GA seems to be efficiently used in multilevel surgery for treatment of hypopharyngeal airway impairment. Current research aims to optimise the identification of proper
candidates for this surgery. Further studies are needed to identify an optimal strategy for targeted treatment of severe OSAS patients. GA cannot be recommended as a single procedure for the surgical treatment of OSA (C).

2.4.2. Maxillo-mandibular advancement

Rationale
This surgery specifically addresses hypopharyngeal or tongue base obstruction in order to enlarge the retrolingual and retropalatal airway. An advancement of 10 to 15 mm of the maxilla and the mandible is necessary to be efficient when there is no maxillomandibular abnormality. In case of maxillomandibular abnormality the advancement must be more pronounced. The classical procedure consists in bilateral sagittal split ramus osteotomies with rigid internal fixation and Lefort I osteotomy with rigid internal fixation [305-316]. The Stanford group [305] performs pharyngoplasty with or without hyoid myotomy suspension (phase I). MMA is performed in second step (phase II) in case of failure of phase I. The rationale for using phase I is to avoid more radical and high-risk surgery when unnecessary, particularly in moderate OSA. Conversely, other groups proceed directly to MMA. Sometimes mandibular elongation using osseous distraction followed by a Le Fort I advancement osteotomy is an efficient solution for difficult situations in order to obtain an easy advancement of 12 to 14 mm in 3 weeks [317]. This procedure needs a close communication with the orthodontist. Successful surgery depends on proper patient selection, proper procedure selection and experience of the surgeon [197, 318].

Search criteria
Data bases individually searched: PubMed and Medline. Keywords combinations: maxillomandibular advancement and sleep, maxillomandibular advancement and obstructive sleep apnea, orthognathic surgery and sleep.
Overview of the evidence

The level of evidence is based on 12 series published between 1989 and 2006 (table e31) [305-316]. The baseline AHI varied between >20 and >30, success was defined by a postsurgical AHI between <10 and <20. The mean follow-up was performed between 6 weeks and 52 months. The success rate varied between 67% and 100% [305-307]. The discrepancy can be explained by different polysomnographic techniques [305-307]. A quarter of the remaining respiratory abnormalities are central events [306]. All series, including 298 patients, demonstrated an improvement of postoperative sleep macrostructure (table e31) [306-308]. Changes in Excessive Daytime Sleepiness and Multiple Sleep Latency Test after MMA were rarely documented.

Prinsell [307] demonstrated a lowering of systolic and diastolic blood pressure after MMA, associated with weight loss. Riley and al [305] reported that >50% of the patients treated by MMA no longer require antihypertensive medicines. However, there are no sufficient data on the efficacy of MMA on cardiovascular parameters.

In all series, patients usually undergo MMA surgery only after a complete clinical and cephalometric examination to evaluate the three major anatomic regions of potential upper airway obstruction: nose, palate (oropharynx), and base of tongue (hypopharynx) [305-316]. In some cases presurgical evaluation is performed by a multidisciplinary team including a maxillofacial surgeon, a neurophysiologist and a pulmonologist [308, 314]. Selected patients are often male patients with an AHI >30, an age <60 years old, a BMI <30 kg/m², without relevant cardiovascular and pulmonary co-morbidities (table e31).

All patients have to undergo overnight polysomnography according to widely accepted methods [319]. Alternatives to in-laboratory full polysomnography, especially in-home monitoring without EEG analysis, are not used due to insufficient detection of hypopnoeas or central events.

Bettega [308] identified hypertrophic tonsils in 40% and hypopharyngeal obstruction at the tongue base in 80% of the surgical candidates. This is generally explained by
small oral cavities with a normal tongue size. All patients performed cephalometry before undergoing MMA in the 12 series (table e32). However, the results of the cephalometric analysis are not always reported [308]. OSA patients may present with pharyngeal narrowing at basal lingual level, sometimes in combination with retrognathia (SNB less than 77°) or dolichofacial appearance [320]. Patients with a BMI <30 kg/m² have shorter anterior floor of cranial base, a smaller mandible and retroposition of the mandible compared with severely obese patients [321]. These skeletal differences are associated with narrower velopharyngeal and linguopharyngeal spaces predicting better surgical success. There is no sufficient evidence whether successful treatment by mandibular advancement devices is predictive for successful MMA surgery.

Several complications have been reported, including cardiac arrest without sequellae and dysrhythmia [310], local infection, perforation of the palate, a maxillary pseudarthrosis, malocclusion, dysgnathia due to mandibular deficiencies [305-309, 311-314]. All patients developed transient anesthesia of the cheek and chin area. Residual neurosensitive deficit (hypoesthesia of the lower lip) was the most common complication which did not affect quality of life in these patients. Patients who have a prior pharyngoplasty have temporary postoperative velar insufficiency (phonetic deficit and liquid regurgitation) improved by cautious speech therapy. Most of the patients accept changes in facial appearance, which can be predicted by preoperative computer imaging. The average off-work time post operative is between 2 weeks [307] to 10 weeks [308, 309]. An in-laboratory full polysomnography has to be performed between 2 and 6 months after surgery.

MMA has been shown to be effective over the long term [311, 322-324]. While Waite et al [310] confirmed long-term skeletal stability (12 months) based on cephalometric analysis, Pepin [325] and Li [92, 197, 311-329] demonstrated a deterioration of the results with a rate of success of 60% on a long term basis. Aging and weight gain appear to significantly impair long-term results

Conclusions and recommendations
MMA seems to be as efficient as CPAP in patients with OSA who refuse conservative treatment [330], particularly in a young OSA population without
excessive BMI or other comorbidities. Therefore, MMA is recommended in this selected group of patients. However, essential benefit should be weighed against the risk of complications. The one-time cost of early MMA is probably far less expensive than multiple less successful surgeries or lifetime use of CPAP. Current research aims to optimise the identification of proper candidates for this surgery (B).

2.4.3. Distraction osteogenesis

Rationale
Distraction osteogenesis (DOG) is a surgical procedure applied in order to provide a lengthening of the bone associated with a stretching of the soft surrounding tissues [331]. Bone is osteotomised, and after a latency period, the device is activated progressively (about 1mm/day) to induce bone healing and new bone formation. DOG can provide wide expansion and is thus very useful to correct severe maxillofacial anomalies in young children [332]. The procedure is used in different etiologies of OSA especially in pediatric craniofacial malformations.

Search criteria
Data bases individually searched: PubMed and Medline. Keywords combinations: distraction osteogenesis and sleep, distraction osteogenesis and obstructive sleep apnoea, surgery and sleep, surgery and obstructive sleep apnoea.

Overview of the evidence
Most of the articles are focused on mandibular DOG in pediatric micrognathia (table e33) (39 publications) [197, 317, 331-371]. They include several case reports and some retrospective and prospective series. The level of evidence remains low in such series (2b–4) with short series, lack of complete objective assessment, undefined criteria for patient selection and short-term follow-up. Only 8 articles, from 1998 to 2009, were selected as they met the following criteria: mandibular lengthening in micrognathia, the confirmation of the diagnosis of sleep apnoea syndrome and objective evaluation of the benefit of the treatment. Other publications provide, however, interesting evidences of DOG benefit on children’s respiratory status in order to avoid tracheostomy or to remove it.
DOG is used in craniofacial disorders associated with severe airway impairment as a result of micrognathia or midface hypoplasia. Retrusion of the inferior third of the face with micrognathia (Pierre Robin Sequence, bilateral hemifacial microsomia (due to growth disturbance of the mandibula), Treacher Collins syndrome, Nager syndrome, TMJ ankylosis) might require mandibular advancement [336, 337, 347, 348, 356, 357, 365, 369]. Airway impairment is localised in retroglossal area. Retrusion of the upper third of the facial skeleton (Midface hypoplasia and retrusion) may need maxillo-zygomatic advancement (Lefort III or Monobloc advancement). In this case, airway impairment is localised on velopharyngeal area. Syndromic faciocraniosynostosis (such as Crouzon, Apert or Pfeiffer syndrome) induce midfacial retrusion with velopharyngeal tissue obstruction [335]. The benefit on morphological improvement is associated with an enlargement of the posterior airway space. In significant numbers of these patients, tracheostomy is indicated when obstruction remains refractory to conservative management (particularly in neonates). But tracheostomy also provides significant morbidity and mortality (0 to 3%) in young patients. Thus, in selected children, DOG is proposed to prevent tracheostomy or to achieve decannulation.

Indication of DOG remains controversial [354], particularly in non syndromic micrognathia and Pierre Robin Sequence. Non-surgical handling in mild obstruction permits improvement in an important majority of cases [354], because of sufficient mandibular growth potential [351] and increase of tongue neuromuscular tone [365] within the first year of life. The review of literature underlines the efficacy of DOG in OSA and breathing difficulties. However, there is no consensus on precise indications and timing of the procedure. Because of potential complications of DOG in neonate period, some authors avoid DOG in the first months [354, 357], and apply delayed distraction to decanulate tracheostomised children after 18-24 months [357]. In contrast, other authors use DOG in the first months of life in severe cases to avoid tracheostomy [341, 352, 364, 371]. Genecov et al. [368] studied 81 patients with mandibular micrognathia (mostly PRS) and airway obstruction syndrome over 11 years (mean age 1.2 y). Tracheostomy was prevented in 96%, and decannulation achieved in 92%. AHI decreased from 35-50 to 5-15 in 65 patients (2 remained >35). The airway benefit of the DOG was evaluated by cephalometric analysis and 3D-CT
in several studies [341, 356, 369]. Cross-sectional space and skeletal lengthening increased significantly.

Faciocraniosynostosis (Crouzon, Apert or Pfeiffer syndrome) induce midfacial retrusion leading to variable sleep related breathing disorders due to velopharyngeal obstruction in young patients and adults [339]. Midface advancement can relieve the obstruction and thus decrease sleep apnoea events and also lead to decannulation of tracheostomised patients. DOG can provide large magnitude advancement of the facial skeleton by progressive stretching of all the surrounding tissues compared to one-stage procedures. Two types of osteotomies can be performed: Lefort III osteotomy (advancement of facial skeleton without cranial shape correction) or monobloc osteotomy (frontofacial advancement) within the first years of life. However, there are only few publications analysing the benefits on upper airway obstruction (table e34). There is less evidence on the efficacy of midface advancement on airway obstruction as compared to mandibular lengthening (C).

Numerous reports have demonstrated that DOG is also effective in adults [317], but it remains currently an optional treatment in selected patients (e.g. in TMJ ankylosis sequelae [347], in facial cleft lip/palate sequelae). The procedure is limited by the risk of malocclusion due to incorrect distraction vectors paralellism, the length of the procedure, incomfort of the device. Actually maxillomandibular advancement (MMA) can be provided in a single stage, without need of bone graft with a good stability and efficiency.

**Conclusions and recommendations**

Although there are only few publications to correctly evaluate its benefits, DOG is usefully applied and can be recommended in congenital micrognathia or midface hypoplasia. These indications may increase in the future, with less invasive procedures and adapted devices. Controversies however exist on early use to avoid tracheostomy in micrognathia. DOG may be indicated in selected adults or adolescents as MMA is surgically difficult to achieve. The efficiency of distraction advancement in OSAS treatment can be scored B in mandibular lengthening and C in midface advancement.
2.4.4. Multilevel surgery

Rationale
Most of OSA patients have multilevel disease including nasal obstruction, retropalatal and hypopharyngeal obstruction. The goal of multilevel surgery (MLS) is to improve nasal airway blockage and both to enlarge the retropalatal airway and the retrolingual airway. At least surgery aims to correct anatomical abnormalities in the upper airway (UA) contributing to its collapse in the hypopharyngeal space during sleep. Nasal reconstructive surgeries include septal and/or bony intranasal reconstruction, alar valve or alar rim reconstruction and turbinectomy. UPPP, often combined with adenotonsillectomy, aims to trim and reorient the posterior and anterior lateral pharyngeal pillars by excising the uvula and the posterior portion of the palate. Mandibular osteotomy with genioglossus advancement (GA), hyoid myotomy suspension (HS), laser midline glossectomy with lingualplasty, and radiofrequency tongue base reduction (RTBR) aim at enlarging the retrolingual space.

Search criteria
Data bases individually searched: PubMed and Medline. Keywords combinations: multilevel surgery and obstructive sleep apnea, multilevel surgery and sleep, surgery and sleep

Overview of the evidence

Overview of the evidence
Sundaram et al [48] recently reviewed the literature on surgery for OSA. No randomised trials could be identified. The authors emphasised methodological difficulties: variety of outcome measures, lack of long-term follow-up data, lack of consensus on the definition of “surgical success”. The result of MLS efficiency was not reproducible in different studies. However, Lin and Friedman [389] focused on outcomes of OSA patients treated with MLS in a meta-analysis of 49 studies.
including 1978 patients with a mean follow-up time of 7.3 months. The recalculated success rate was 66.4% with an overall complication rate of 14.6%.

Studies evaluated here differed in terms of the preoperative AHI between >5 and >30, the definition of success (postsurgical AHI <10 to <20) and follow-up (6 weeks to 39 months) [373, 374, 383, 385] (Table e35). Success rate varied between 22.7% to 78% (mean 60.9) [299, 308]. Only Riley [376] and Chabolle [286] reported a significant improvement in SWS and REM sleep after MLS (Table e36). The microarousal index or ESS scores were rarely reported by the authors [281]. There is no evidence of improvement in cardiovascular parameters after MLS.

As CPAP is the standard treatment for adult OSA, all attempts of improving effectiveness and adherence have to be performed prior to undergo MLS. However, MLS may be considered in younger OSA patients in whom CPAP is unsuccessful or has been rejected for a long term period.

In most of the series, patients usually undergo MLS surgery only after nasofibroscopy and a complete clinical and cephalometric examination to evaluate the three major anatomic regions of potential upper airway obstruction: nose, palate (oropharynx), and base of tongue (hypopharynx) [243, 273-275, 277, 281, 284-286, 288, 289, 291, 295, 299, 308, 313, 316, 372-388]. The Friedman staging system [275] is necessary to score the palate position and the tonsil size. In some cases, presurgical evaluation is performed by a multidisciplinary team, including a maxillofacial surgeon, a neurophysiologist and a pulmonologist [308]. Severity of OSA disease was not a criterion for exclusion. Selected patients are often male, have an AHI >20, age <70 years, a BMI <40 kg/m² (Table e37). Patients with a history of respiratory or cardiac failure during the past year are excluded from performing MLS [299]. For Bettega et al. [308] all OSA patients undergoing a MLS have to be non-smokers or have quitted smoking at least one month prior to surgery. At least patients with obvious micrognathia, bony anatomic abnormalities, without obvious palatal obstruction and patients who had previously failed surgical treatment with UPPP are thought to respond insufficiently to MLS.
All patients have to undergo overnight polysomnography prior to MLS surgery [319], which allows for detection of REM-related OSAS. MLS seems to be more effective in REM OSA patients. Kao et al [386] reported a 100% success rate in patients with AHI <30 treated by MLS. It dropped to 50% in patients with AHI >50. Liu et al [388] observed a higher success rate for OSA patients with an apnoea index <25. Eun et al [374] observed a significant improvement of postoperative AHI after MLS (UPPP and RTBR) in 28 REM OSA patients (8.1 ± 6 versus 14.5 ± 7; p<0.001), while there was no change in 62 non-REM OSA patients (21 ± 21 versus 23.1 ± 10; p=0.374).

The success rate of MLS on AHI is about 53.6% at 6 months according to the analysis of the results of the 1431 patients who underwent MLS. Vicente [299] studied the long-term efficacy of UPPP and HS for severe OSA and reported a 78% success rate at 3 years after MLS surgery. Neruntarat [243] observed the same results at 39 months for 49 OSA patients treated by UPPP and GA. Andsberg [285] observed the same results at 8 years.

Bettega et al. [308] identified hypertrophic tonsils in 40% and hypopharyngeal obstruction at the base of tongue in 80% of the surgical candidates. This is generally explained by small oral cavities with a normal tongue size. Cephalometry was performed in most of the patients before undergoing MLS in the 32 series (Table e38). Patients with a BMI <30 kg/m² have shorter anterior floor of cranial base, a smaller mandible and retroposition of the mandible compared with severely obese patients [321]. These skeletal differences are associated with narrower velopharyngeal and linguopharyngeal spaces and predict better efficacy of MLS. Some authors [299, 388] performed the Muller maneuver during cephalometry to predict hypopharyngeal collapse. However, as cephalometric radiographs did not differ between responders and non responders to MLS, hence, they are unable to predict surgical success.

A wide variety of side effects can occur after MLS surgery, including velopharyngeal insufficiency, dysphagia, persistent dryness and nasopharyngeal stenosis (UPPP, uvuloflap), mandibular fracture, lesions of the roots of the teeth, infection, permanent anesthesia of the lip and seroma (GA), odynophagia, postoperative oedema or excessive bleeding, often associated with incised epiglottis, requiring a protective
tracheotomy (partial glossectomy), tongue restriction (lingualplasty) [288]. Many patients have had subjective alterations in taste immediately postoperatively, which resolved spontaneously. Rare complications included angina pectoris [382], dysphagia and cricopharyngeus, hematoma of the mouth floor [377], long-lasting hypoglossal nerve paresis [375].

**Conclusions and recommendations**
MLS cannot be recommended as a substitute for CPAP but as a salvage procedure for OSA patients in whom CPAP and other conservative therapies failed. Surgical success of MLS for OSA is often unpredictable and less effective than CPAP. MLS seems to be more effective in mild to moderate REM-associated OSA, in patients <60 years, BMI <30 kg/m², pharyngeal narrowing in the basal lingual area, retrognathia or dolichofacial appearance and without significant comorbidity. Success depends on appropriate patient selection, the type of surgical procedure performed and the experience of the surgeon. Most studies are retrospective and observational case series, and therefore do not provide high-level evidence (C). Further research should include larger, higher level studies that compare surgical procedures and identify factors associated with outcomes.
Acknowledgements

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References


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<td>1a</td>
<td>Systematic analysis (Systematic Review, SR) of randomised controlled studies (RCT) with homogenous results</td>
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<td>1b</td>
<td>Particular RCT with limited dispersion</td>
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<tr>
<td>1c</td>
<td>Therapy, before its introduction mortality in all patients</td>
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### Table 2: Grades of recommendation

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<tr>
<td>B</td>
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<tr>
<td>C</td>
<td>Level 4-studies or extrapolations of level 2- or 3-studies</td>
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<tr>
<td>D</td>
<td>Level 5- or inconsistent studies of other levels</td>
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