

## **Management of Obstructive Sleep Apnea**

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### **ABSTRACT**

Obstructive Sleep Apnea (OSA) is an important public health problem and is associated with considerable morbidity and mortality. Therefore, treatment of this condition is of paramount importance. The treatment of OSA includes general and behavioural measures, mechanical measures including continuous positive airway pressure (CPAP), Bilevel positive airway pressure (BiPAP) and Oral Appliances (OA), pharmacological treatment and surgical procedures. Continuous positive airway pressure (CPAP) treatment reverses the repetitive upper airway obstruction of sleep apnea and associated daytime sleepiness and is the most effective treatment for OSA. However maintaining patient adherence to CPAP therapy is a challenge. Weight loss should be recommended to overweight patients with OSA, as it has been shown that weight reduction has additional health benefits. Treatment of underlying medical conditions such as hypothyroidism or acromegaly has profound effect on apnea/hypopnea index. A subset of patients with OSA may benefit from supplemental oxygen and positional therapy. Presently, there are no effective pharmacotherapeutic agents for treatment of patients with OSA and the role of surgical treatment in OSA is controversial. However, pharmacological treatment of persisting residual sleepiness, despite adequate positive airway pressure therapy delivery and adherence, is indicated and may improve daytime sleepiness.

*Key words* : CPAP, Oral appliances, Modafinil, CPAP compliance  
Uvulopalatopharyngoplasty, positional therapy

## INTRODUCTION

There are several consequences that are associated with obstructive sleep apnea (OSA) (1). Life threatening cardiovascular complications can occur in patients with OSA. The treatment of OSA is of utmost importance not only to prevent serious consequences, but also to improve the quality of life of such individuals. The treatment of OSA includes general and behavioural measures, mechanical measures including continuous positive airway pressure (CPAP), Bilevel positive airway pressure (BiPAP) and Oral Appliances (OA), pharmacological treatment and surgical procedures.

### General and behavioural measures :

General measures include weight reduction, avoidance of alcohol at least 4 to 6 hours prior to bed time, avoidance of sedative drugs that are known to make apnea worse, smoking cessation, sleeping on one's side rather than on the back or stomach and avoiding sleep deprivation. As obesity is an important factor in the causation of OSA, it has been observed that a 10% reduction in weight was associated with clinically significant improvement in apnea-hypopnea index (2, 3). There are several benefits from reduction of weight in OSA and these include decrease in respiratory disturbance index (RDI), lowering of blood pressure, improvement in sleep structure and snoring and improvement in pulmonary function and arterial blood gas values. There is also a possibility that

weight reduction may reduce the optimum CPAP pressure required. Longitudinal studies are required to assess the long-term effects of methods of weight loss (e.g. bariatric surgery and carbohydrate-restricted diets) on the severity of OSA (4, 5).

### Mechanical measures :

Mechanical measures include positive airway pressure with a CPAP or bilevel positive airway pressure (BiPAP) and oral appliances (OA). The standard treatment of OSA is with CPAP. The treatment of OSA should start from least invasive and effective to most invasive and effective. All patients with OSA should be offered nasal CPAP first. Patients with mild-to-severe OSA who refuse or reject CPAP therapy may be offered the next choice, i.e. BiPAP therapy. If BiPAP therapy also fails, OA therapy may be considered (5). Oral appliances can be the first line therapy in mild OSA, if they are unwilling to use CPAP.

#### a) CPAP therapy :

CPAP therapy is the first-line standard of care for treating OSA and this is the only intervention shown to have a favourable impact on both cardiovascular and neurobehavioral morbidities. A "pneumatic splint" is created by delivering a fan-generated flow and thus CPAP maintains airway patency. CPAP dramatically reduces or eliminates apnea and hypopnea in most patients (6). The effectiveness of CPAP depends on the

utilization of the machine and mask by the patients. Approximately, 25-50% of patients either will refuse CPAP therapy or cannot tolerate it. Of the patients who accept CPAP, about 40-60% of them continue to use it for one year or longer. Nonadherence to the use of CPAP is therefore a major therapeutic challenge. When adherence is defined as greater than 4 hours of nightly use, 46 to 83% of patients with obstructive sleep apnea have been reported to be nonadherent to treatment. Evidence suggests that use of CPAP for longer than 6 hours decreases sleepiness, improves daily functioning, and restores memory to normal levels. No single factor has been consistently identified as predictive of adherence. Emerging data suggest that various behavioural interventions may be effective in improving CPAP adherence (7, 8).

Patients who have been diagnosed as having OSA and who require CPAP treatment, have titration of pressure over an entire night (full-night polysomnogram (PSG) titration) during a technician-attended PSG. Titration is usually done by a trial and-error process and the technician adjusts the applied pressure until respiratory and sleep parameters that are considered to be clinically important are reduced to the degree judged by the clinician to be acceptable (9). The pressure needed typically is 5-20 cm H<sub>2</sub>O. Auto adjusting CPAP (A-CPAP) devices are intended to detect breathing disturbances or absence of such disturbances over specified intervals and modify the applied positive airway

pressure upward or downward, respectively, in real time, according to a device-specific algorithm. Split-night PSG titration is an attended, in-laboratory, overnight procedure during which sleep and breathing variables are recorded for diagnostic purposes during the first hours of the sleep period, after which, if specific criteria are met, CPAP titration is performed during the remainder of the night. Split-night PSG titration may provide a pressure prescription that is comparable to that of full-night PSG titration in patients who demonstrate frequent obstructive events early in the sleep period (6). Patients with moderate to severe sleep disordered breathing (apnea-hypopnea index greater than 15) should be treated with CPAP irrespective of their symptoms because these patients are at increased risk of cardiovascular morbidity. Patients with mild form of OSA (AHI 5 to 14.9) can be treated with CPAP if they have one of the following i.e. excessive daytime sleepiness, hypertension or coexistent cardiovascular disease. Conventional CPAP therapy applies fixed pressure continuously to the patient. Since respiration is a dynamic process applying a fixed pressure continuously may not be appropriate. Therefore, CPAP devices are currently available that automatically change pressures based on the presence and/or absence of OSA (auto-positive airway pressure, auto-PAP). CPAP has been reported to improve daytime sleepiness, cognitive function and quality of life and also has been found to decrease blood pressure and health care costs (6). Important drawback of CPAP therapy is

the poor adherence to CPAP therapy. Many patients do not accept CPAP devices and many do not regularly report for follow up visits (8). Complications of CPAP therapy include a sensation of suffocation or claustrophobia, musculoskeletal discomfort, aerophagia and sinus discomfort. Rarely pneumothorax, pneumomediastinum and tympanic membrane rupture have been reported.

#### ***b) BiPAP Therapy :***

Whereas CPAP delivers a constant pressure during both inspiration and expiration, BiPAP allows independent adjustment of the pressures delivered during inspiration and expiration. BiPAP therapy is prescribed in patients with OSA who cannot tolerate high CPAP pressure or have complications following CPAP therapy i.e. ear infections, bloating etc. (5). There is no distinct advantage of BiPAP over CPAP therapy.

#### ***c) Oral appliances :***

The indications for oral appliances are OSA patients with mild-to-moderate OSA who prefer OA to CPAP therapy, who do not respond to CPAP therapy and in whom the CPAP therapy had failed. Therefore OA is not indicated in patients with severe OSA (5). There are three basic designs of OAs. These are mandibular repositioners, tongue retaining devices and palatal lifting devices. There are more than 40 OAs available to manage sleep related breathing disorders and

obstructive sleep apnea. Contraindications to the use of OAs are less number of teeth, patient is unable to protrude the mandible forward and open jaw widely, pre-existing temporomandibular joint problems, severe bruxism and patients with full dentures. Complications of oral appliances include excessive salivation, dental misalignment with bite change, temporomandibular joint disease, gum irritation, salivation and tongue pain (5).

#### **Pharmacologic treatment :**

##### ***a) Serotonergic agents :***

It has been observed that serotonin contributes to upper airway patency and that serotonergic agent reduces sleep-related breathing events both in rapid eye-movement (REM) and non-REM sleep in an animal model of OSA. Selective serotonin reuptake inhibitors (fluoxetine and paroxetine) have been shown to decrease apnea-hypopnea index (10). Mirtazapine is a piperazinoazepine-derivative tetracyclic antidepressant and is also a 5-HT antagonist. It is thought to act as a central ventilatory stimulant as it has effects at noradrenergic and histaminergic receptors. Though it has been shown to reduce AHI by almost 50%, its antihistaminergic properties compromises its utility in OSA. It causes weight gain in many subjects. However these selective serotonin reuptake inhibitors are not currently recommended for treating OSA.

***b) REM suppressants :***

As atonia is a feature of rapid eye movement (REM) sleep interfering with thoraco-abdominal muscles of respiration, REM suppressants have been suggested as therapeutic agents for treatment of OSA. A subset of patients develops OSA and hypopnea events almost exclusively during REM sleep. These patients may be candidates for REM suppressant therapy. It has been observed that many drugs including fluoxetine, paroxetine, tricyclic antidepressants, alcohol and stimulants (dextroamphetamine) have REM-suppressing effects. Two other REM suppressants evaluated for treatment of OSA are protryptiline and clonidine. Protryptiline is a tricyclic antidepressant having anticholinergic, serotonin and noradrenergic reuptake inhibitory effects. Protryptiline has been found to significantly reduce apnea/hypopnea index (AHI), however there was no reduction in REM AHI. Though protryptiline may reduce AHI, the reduction is not sufficient to recommend its use in OSA. Clonidine is a noradrenergic  $\alpha_2$  agonist and is used as an antihypertensive drug. Clonidine was evaluated for the treatment of OSA because of its REM suppressant effect. However, clonidine is not recommended for treatment of OSA as it has major side effects such as CNS depression and orthostatic hypotension (11, 12). The effectiveness of REM suppressants in the treatment of OSA is not determined (10).

***c) Ventilatory stimulants :***

Methyl xanthines, opioid antagonist (naloxone), doxopram and nicotine are the drugs evaluated as ventilatory stimulants for treatment of OSA. Nicotine is used as a smoking cessation drug and it has both CNS and respiratory stimulant effects. However none of these drugs are having promising effects to be recommend for OSA treatment (13, 14).

***d) Wake promoting substances (e.g. Modafinil and armodafinil) :***

Despite treatment with CPAP, many patients demonstrate residual sleepiness. Wake promoting substances are advocated as an adjunctive treatment for such residual sleepiness. Modafinil is a wake-promoting agent which has been approved for the treatment of narcolepsy. Modafinil was therefore evaluated in patients with excessive daytime sleepiness and this drug has no effect on AHI. In a randomized, double blind, placebo-controlled parallel group trial, modafinil was evaluated in a group of patients who were treated with CPAP and with residual sleepiness (dose 200 mg/day week 1 and then 400 mg/day weeks 2-4). It was observed that modafinil significantly improved daytime sleepiness (15). The common adverse events are headache, nausea and infection. It has been reported that life-threatening skin reactions may occur with modafinil. Other adverse events reported are psychiatric symptoms. Modafinil may be given to adult patients with OSA having excessive somnolence

despite well treated with CPAP (10).

***e) Hormonal treatment :***

There are no randomized prospective studies that have evaluated hormonal replacement (e.g. Medroxyprogesterone and oestrogen) treatment on prevention of OSA. It has been hypothesized that increased incidence of OSA in postmenopausal women is due the loss of protective effect of estrogen and progesterone. Several studies evaluated the role of these hormones in the treatment of OSA. However, there are no consistent data to show the beneficial effects from hormone replacement treatment in OSA (16).

***f) Endocrinological disorders :***

*i) Thyroid hormone replacement therapy :*

Hypothyroidism is an important risk factor for development of OSA. All patients with OSA require evaluation to exclude hypothyroidism. . Thyroid hormone replacement therapy completely reverses OSA due to hypothyroidism. Reversal of OSA in such situation may take one year (17).

*ii) Growth hormone suppressant therapy in acromegaly :*

Patients with OSA may require evaluation for acromegaly as it is associated with OSA. If acromegaly is suspected, such patients require

appropriate endocrine evaluation. Bromocriptine and octreotide (a somatostatin analog) have been found to significantly reduce AHI in patients with acromegaly (18, 19).

***g) Supplemental Oxygen :***

Intermittent hypoxia has been implicated as the underlying mechanism for the systemic manifestations seen in OSA. Supplemental nocturnal oxygen therapy was evaluated in patients with OSA. It was observed that oxygen administration improved nocturnal oxygen saturation levels but does not improve airway patency (20).

***h) Improvement of nasal patency :***

Patients with OSA and coexisting rhinitis may benefit from the use of nasal corticosteroids. However this alone will not be sufficient to treat OSA (21).

***I) Positional therapies :***

Lateral positioning therapy has been found to improve AHI (22). Use of specially designed pillows to improve neck and body position in sleep requires further evaluation (23).

***j) Antioxidants :***

An imbalance in the oxidant-anti-oxidant status has been implicated in the development of cardiovascular abnormalities in patients with OSA. There is not only an increase in pro-oxidants but

also a decrease in anti-oxidants. It is recognised that when there is oxidative stress, there is an increase in the production of the inflammatory cytokines which in turn would produce further free radicals, thus forming a vicious cycle and worsening the disease condition. Oral N-acetylcysteine (NAC), an antioxidant, administration appears to have a therapeutic potential in the treatment of OSA (24). Compared to a previous investigation in which the anti-oxidants used were vitamins E and C, there was a greater increase in total reduced glutathione (GSH) level in the NAC group (24, 25).

### **Surgical Treatment :**

The role of surgery in the treatment of OSA is controversial. Patients with reversible upper airway obstruction such as adenotonsillar hypertrophy or mass lesions are candidates for surgery with beneficial effects. Uvulopalatopharyngoplasty is a commonly performed surgery in OSA in which soft palatal tissue is excised, but with suboptimal results (26). Mandibular advancement devices have been found to be effective in mild apnea and may improve daytime symptoms (27). Other surgical procedures attempted for treatment of OSA are septoplasty, nasal polypectomy, radiofrequency ablation of turbinates, uvulopalatal flap, palatal advancement, radiofrequency ablation of the soft palate, genioglossal advancement, hyoid suspension, partial glossectomy, tongue radiofrequency ablation,

lingualplasty, maxillo-mandibular advancement and epiglottoplasty. It has also been reported that bariatric surgery may be useful. However, there are no randomised trials showing the efficacy of bariatric surgery in OSA. Tracheostomy, though very effective in the treatment of OSA, is a disfiguring procedure and decreases the quality of life of the patients. Tracheostomy is therefore reserved for patients with severe OSA in whom other medical and surgical procedures have failed (5).

### **Hypoglossal Nerve Stimulation :**

Since hypoglossal nerve stimulation (HGNS) recruits lingual muscles and reduces pharyngeal collapsibility, it is possible that stimulation of hypoglossal nerve may be used to treat sleep apnea. A Hypoglossal Nerve Stimulation System (HGNS) was implanted in patients with OSA to test this hypothesis. It has been shown that hypoglossal nerve stimulation produced marked dose-related increases in airflow without arousing patients from sleep, suggesting that hypoglossal nerve stimulation is a potential novel therapeutic approach for patients with OSA (28).

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