REVIEW ARTICLE

Novel Therapies in the Treatment of Obstructive Sleep Apnea

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Abstract

There is an effort on several fronts for newer effective therapy for obstructive sleep apnea. This is because, till now the two main modalities of therapy, continuous positive airway pressure therapy or use of various oral appliances are fraught with problems of poor acceptance and long time adherence. Though numerous modalities have been tried which are discussed in the review, there are few novel approaches which hold great promise as probable effective modalities for the future. In children, the simplest cost effective treatment undoubtedly remains a well timed adeno-tonsillectomy which could as well be curative. However, a high flow open nasal cannula based positive airway pressure therapy has been found to be effective in mild and moderately obese children. In adults, oral pressure therapy using an external suction apparatus connected to an intra oral device, that increases the retropharyngeal space and prevents the tongue from falling back, has been found to be effective in initial studies. Stimulation of the genioglossus by hypoglossal nerve pacing with the use of a pulse generator placed in the infraclavicular region is another promising modality. Various new surgical techniques specially the maxilla mandibular advancement procedures and computerized surgical planning methods hold great promise. Lastly, the multimodality approach using the new knowledge on the pathophysiology of sleep apnea is likely to be the therapy for the future.

Keywords: obstructive sleep apnea, continuous positive airway pressure, genioglossus, apnea hypopnea index (AHI)

Introduction

The Wisconsin-based cohort study of state employees younger than 65 years of age found a prevalence of sleep-disordered breathing (SDB) to be 9% in women and 24% in men. The *sleep apnea syndrome* defined as the presence of both SDB and self-reported sleepiness and characterized by recurrent collapse of the upper airway during sleep was present in 2% of women and 4% of men[1]. Obstructive sleep apnea (OSA) is now an increasingly common sleep disorder, with moderate to severe disease evident in 17% of men and 9% of women in the middle aged population[2]. Some studies have reported the prevalence of OSA to be between 9-28% in women and 24-26 % in males, qualifying it as one of the commonest sleep and pulmonary disease having serious public health consequences[3]. OSA not only affects the quality of life

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(QOL) of the individual but also has serious health consequences and is believed to increase heart diseases, strokes, hypertension, diabetes, increased mortality and results in a huge economic loss. However, what is probably more disturbing is the number of accidents resulting from untreated OSA's, leading to disability or death of the individual and innocent fellow travelers and motorists[4,5]. Sleep disordered breathing has partially been held responsible for several catastrophes like the Three Mile Island, Chernobyl and The Exxon Valdez disasters.

Usual Modalities for the Treatment of OSA

Weight loss: Obesity is one of the major risk factors likely to contribute to OSA through directly compromising pharyngeal airway space by adding to the surrounding tissue mass, particularly through enlargement of the parapharyngeal fat pads and fat deposited in the tongue[6,7].

It is known that 70% of people of OSA are overweight or obese and weight loss can significantly improve the severity of OSA, AHI, QOL and reduce collapsibility of the passive pharynx[8]. A recent update from the Wisconsin Cohort Study has shown an increased prevalence in OSA which is correlated with an increase in BMI[2].

In another community based Wisconsin Sleep Cohort, a 10% decrease in weight was shown to be associated with a 26% reduction in AHI[9]. Another recent randomized control trial showed that loss of weight alone caused greater improvement in cardio metabolic risk factors than CPAP[10] Obesity is the strongest known risk factor for OSA and besides other effects it also reduces lung volume, particularly in the supine position[11] Lung volumes fall during sleep and in the recumbent position[12]. Decrease in lung volume improves upper airway patency, reduces its collapsibility, airflow resistance and increases pharyngeal cross-sectional area[13].

Bariatric surgery: helps in loss of weight among individuals who otherwise are unable to lose significant weight through diet and exercise programs. In a recent trial, OSA patients lost an average of 27.8 kg in 2 years with a concomitant reduction in OSA severity after bariatric surgery, compared to conventional weight loss (weight loss 5.1 kg). Bariatric surgery patients were found to have lost more weight but their sleep apnea was not reduced by an amount greater than diet alone[14].

CPAP therapy: Currently the most effective therapy for OSA is the use of continuous positive airway pressure (CPAP) therapy during sleep, which splints the upper airway[15] It is the gold standard treatment for OSA but is limited by poor acceptance and adherence[16]. The primary reason of poor long term efficacy of CPAP is due to poor compliance. Compliance is also dependent on the benefit from treatment, and incorrect device, interface and pressures are responsible for non adherence which is as high as 50%[17] One third of the patients were seen to have given up CPAP by 5 years. Compliance is also dependent on disease severity and day time sleepiness[18].

CPAP represents a "one size fits all" solution by preventing upper airway collapse. New concepts in OSA pathogenesis and phenotypes have recently emerged and resulted in evolution of novel treatment methods. Randomized controlled study by Bartlett et al compared a group cognitive behavioral therapy (CBT) intervention with a social interaction control on CPAP adherence[19] and found no difference in CPAP adherence. In another randomized controlled study, Deng et al com-pared usual care in newly diagnosed OSA patients with those in whom CBT has been included in addition to CPAP[20]. They found significant differences between groups with regard to use of CPAP.

Newer models of CPAP have been introduced by other manufacturers like the S9™ (ResMed Ltd, Bella Vista, Australia)[21] and Sens Awake® (Fisher and Paykel Healthcare Ltd, Auckland, New Zealand) but under trial conditions showed little advantage over traditional CPAP[22].

Oral appliances (OA): Use of oral appliances for OSA works on the principle of enlarging the pharyngeal airway by mechanical means. The increase in airway size or stiffness is through direct advancement of the tongue or jaw. A number of studies (some controlled) have demonstrated that OA devices are effective in reducing the apnea-hypopnea index (AHI) in mild, moderate, and severe OSA[23,24]. Oral appliances primarily are of two types: (a) mandibular advancement devices which require around 6mm advancement to treat snoring and apnea, (b) tongue retaining devices[25,26,27,28].

Recently, a mandibular advancement device has been developed which can be calibrated like CPAP during a single night PSG, with very good results. It identifies the degree of advancement achieved and can be set as near as possible to the desired goal[29,30]. No significant difference was found between oral appliance and CPAP in treating mild to severe OSAS in a 2 year follow up study[31]. The drop out in oral appliance group was 47% compared to 33% in the CPAP group. Both the groups had similar improvements in PSG and neurobehavioral outcomes. However, CPAP was more effective in lowering AHI and showed a higher SPO2 levels compared to oral devices ($p< 0.05$).

Pathophysiology & Phenotypes of OSA: Although the upper airway structure is likely to be the fundamental abnormality in OSA, no single structural abnormality has been identified in this disorder. There are several anatomic and physiologic abnormalities described. Individual contributions of these abnormalities are not confirmed. It is likely that there is a complex interplay of several factors and not simply an abnormal anatomy. Increased level of pharyngeal collapsibility has to be present for the development of SDB. Also studies show that the obstruction of the upper airway occurs most frequently at the level of the oropharynx (retropalatal and retroglossal)[32] These suggest that there is likely to be a spectrum of different patho- physiologies at play in the production of SDB.

Recently few path breaking studies and reviews have shed light on the possible pathophysiology of OSA[33,34] The study of Eckert et al proposed that anatomically compromised or collapsed upper airway is seen in 81% of cases and is by far the commonest pathophysiological disturbance. However, inadequate responsiveness of the upper airway dilator muscles during sleep is responsible in some for an oversensitive ventilator system control (high loop gain) is responsible in another 36%. In 37% of patients the problem is of premature waking up to airway narrowing. Overall, it is felt that at least one non anatomical factor was evident in 69% of patients, with multiple traits being responsible in 28% of patients. In the review by Eckert[34], factors contributing to the changes in the upper airway muscles, the mechanical properties, factors affecting the size, shape and dynamic function of the upper airway is beautifully illustrated. Termed as physiological phenotyping of OSA, these authors[33] have coined the term, 'Palm Scale', which denotes the role of P Crit (critical pressure), arousal threshold, loop gain and muscle responsiveness scale in the pathogenesis of OSA. The authors attempted to sub classify the traits and hypothesize pathophysiologic factors which interact with upper airway collapsibility and anatomy ultimately determining the presence or absence of OSA and its severity. The three-point PALM scale defined in the study constitutes an important initial step in categorizing individual patients with OSA based on several key pathophysiologic traits. The objective of the PALM scale is to provide a conceptual framework in which to stimulate future hypothesis-driven testing of therapies that target specific underlying mechanisms in individuals[33,35]. It has been noted that numbers of arousal in sleep (arousal index) also result in sleep deprivation and poor quality of sleep by preventing progress to deeper sleep stages. This also promotes ventilatory overshoot, resulting in precipitation of central apneas.

Novel Methods for the Treatment of Osa

Position therapy: A predominantly supine form of OSA is estimated to occur in at least half of all OSA patients. The upper airway is more collapsible in the supine compared to lateral position and this may relate to effects of body position and gravity on airway geometry, upper airway dilator muscle responsiveness and lung volume[36]. Position-dependent sleep apnea is defined as having at least double the AHI in the supine position compared with the lateral position[37].

Older methods for the treatment of positional sleep apnea were crude and uncomfortable (like sewing a tennis ball into the back of the night dress) and had poor long term compliance. Newer devices have been introduced (three axis accelerometer)[38] which are clipped on to the patients and produce vibratory stimulus in the supine position, thereby minimizing sleep in this position and reducing the AHI in sleep. This has been demonstrated to decrease the duration of supine sleep, AHI, apnea index, preventing time of SPO2< 90% in sleep, arousal index and improved sleep quality.

High flow open nasal cannula system for OSA in children: Treatment of OSA in children by the conventional means of CPAP and oral/ tongue retaining devices are fraught with long term developmental issues of the face and bony structures. Mc Cinley et al demonstrated that trans-nasal insufflation(TNI) primarily acts by slightly increasing pharyngeal pressure[39]. Increase in pharyngeal pressure produces increased lung volume to a greater degree in children due to higher chest wall and lung compliance,[40] particularly during REM sleep, when the chest wall musculature is hypotonic. Increases in lung volume might also improve oxygen stores and upper airway patency[41,42,43]. A study was conducted by them[44] wherein children with OSA who were mostly obese, with or without adeno-tonsillectomy, were treated with TNI. The children had a wide spectrum of disease severity. This modality was found useful in a majority of children, with significant reduction of AHI. Also during NREM sleep the prolonged periods of respiratory flow limitation, associated with increased respiratory rates and respiratory duty cycle, were also decreased by TNI. The improvements were noticed in periods of REM as well, that was statistically significant.

For the application of TNI, a flow generator was used to generate a flow of 20 litres/minute of heated, humidified (80%) air[45,46,47,48]. Air was insufflated through a nasal cannula. The response to trans nasal insufflation, though not as effective, was comparable to CPAP in a majority of the patients. Therefore, though adeno-tonsillectomy is the treatment of choice for children with sleep apnea,[49,50,51] TNI might provide an alternative to CPAP and might be a more readily accepted treatment option. It may improve adherence to treatment in children and may ultimately prove more effective in managing the long-term morbidity and mortality of sleep apnea.

Oral pressure therapy: Whereas, use of CPAP opens up the airway in sleep induced collapse by means of positive pressure applied to the nose acting as a pneumatic splint, use of oral pressure therapy, by means of vacuum applied to the oral cavity, ensures that the tongue and soft palate do not fall back to decrease the upper airway lumen in sleep in patients with SDB, with or without anatomic defects[52]. The device has two components, a vacuum generator with a console which is placed outside and an intra- oral device, consisting of mouth pieces of various sizes. These two are connected by means of a tube to transmit the negative pressure. This device was studied by Colrain et al in a multicentre trial for its safety and efficacy in mild to severe patients of OSA[53]. The device has been found to be reasonably well tolerated and used on an average of six hours and has been found to significantly improve the AHI, sleep quality and EDS[53]. In the study sixty three patients of average BMI of 32.4±4.5 were included, OSA varying from mild to severe. All the subjects were pressure therapy naïve patients or patients who had failed CPAP. The device being such that oral breathing is restricted, patients should not to be extremely obese (BMI>40) and must have preserved dentition in each quadrant of the mouth and must be able to breathe easily through the nose. Therefore, this device is not very useful in patients with lingual tonsil hypertrophy or in patients with narrow retroglossal space. Patients should also have at least 4 hours of sleep. Study was done at baseline without device and then repeated on days 1 & 28 with the device. The mechanism of action is depicted very well using CT and 3D rendition[54]. Approximately 31.7% of patients were successfully treated (success being 50% improvement). Side effects were minor and did not warrant discontinuation of therapy. Side effects were found to generally decrease with use. The mouth piece requires replacement every 3-4 months. The benefits over one and three months are also shown in studies by Colrain et al & Schwab et al[54,55]. Subsequently, a device called "Winx+" has been introduced which has a tongue retaining device by modification made in the intra-oral unit of the device, which ensures increased airway volume in the retro palatal region[56].

Nasal positive airway therapy: During the respiratory cycle, upper airway obstruction in sleep begins at the end of expiration, when there is zero flow. At the end of expiration and in inspiration, there is narrowing of the upper airway, resulting in hypopnea/apnea and snoring[57], resulting in decrease in the upper airway cross sectional distance[58,59,60]. CPAP prevents this by pushing air at a fixed pressure which acts as a stent, thereby preventing airway collapse[61,62]. A similar effect was seen to be produced by the use of a nasal EPAP device, which is a single use device based on the principle of a mechanical valve with very low inspiratory pressure of about 1 cm H2O and a expiratory resistance of about 20 cm. It forms a seal around the nose using adhesive material. Two devices have been marketed by the brand names of 'Provent' and 'Theravent'. The likely mechanism of actions are that-PEEP leads to increased end- expiratory volumes and thus increasing the longitudinal traction on the pharynx, making it less collapsible. Dilatation of the upper airway during expiration is maintained until the start of the next inspiration. The mild hypercapnia due to reduced ventilation leads to increased respiratory drive to the upper airway.

In a multi-centric, prospective, case control study conducted by Rosenthal et al[63] to look into the efficacy and 30 days adherence of 'Provent', it was seen that nasal CPAP reduced or normalized the AHI, while improving subjective perception of sleep quality and day time alertness. The results showed considerable heterogeneity in response to the device despite high adherence rates. A subsequent study by Kryger et al[64] which looked at the long term use of nasal expiratory positive airway pressure device as a treatment for OSA, found AHI in the treatment group reduced to 4.7/hour and ESS reduced to 6.0±3.2 from 15.7 and 11.1±4.2 at baseline respectively. The median percentage of nights the device was used all night was as high as 89.3% .A study by Berry et al[65] which was a prospective multicenter, sham controlled, parallel group, randomized, double blind trial, also found that the nasal EPAP therapy to significantly reduce the AHI and improve subjective day time sleepiness, with excellent adherence. However, in a study by Rossi et al[66] which used a CPAP with drawal methodology in a group of OSA patients, with moderate to severe disease where the subjects were put on CPAP after initial evaluation. After 2 weeks of CPAP, they were randomized to continue CPAP or use 'Provent' or placebo. Results showed that OSA recurred in the 'Provent' and placebo group. There was no significant difference compared in the group who continued on CPAP. It was therefore concluded that," 'Provent' cannot be recommended as an alternative short term therapy for patients with moderate to severe OSA, already on CPAP."

Stimulation of genioglossus and neuromuscular therapeutic approaches: Though CPAP is currently the best available mode of therapy for OSA in addition to oral and mandibular devices and life style modification measures, their compliance leaves much to be desired[17]. The role of the pharyngeal dilator muscles in countering the loss of stimulus in sleep was initially hypothesized by Remmers et al . It was found that the major contribution to pharyngeal dilatation is of the genioglossus[67] and was the basis of this alternate mode of therapy of OSA. This was first described by Swartz et al[68] in an animal model and later observations made by Eastwood et al[69] over 6 months. Although initial studies produced conflicting results[70,71] Steier et al[72] showed that use of a sufficiently low current which stimulates the muscle without waking up the patient, could be clinically effective through a study in 11 healthy subjects of near normal BMI (24.5) and in the same number of patients of OSA (BMI-42). The neurostimulator delivers either synchronous [73,74,75,76] or continuous stimulation[77]. The focus of continuous stimulation is to increase tonic, rather than phasic, activation of the genioglossus.In both systems, stimulation periods are maintained on a duty cycle of, 50% to prevent neuromuscular fatigue of the tongue. The contraction of muscle was confirmed ultra sonographically resulting in measurable and significant fall in snoring and improvement of RDI and oxygenation. The study showed the efficacy of this treatment method in patients with mild to moderate increase in BMI. Other studies[78,79] also showed that this method of therapy is not effective in the morbidly obese.

Subsequently, Strollo et al[80] undertook a large multicenter, randomized, prospective study of a single group cohort design in subjects who had issues to either accepting or adhering to CPAP therapy and also evaluated the clinical safety of upper airway stimulation. The implantable stimulation device showed a significant improvement in the AHI, oxygen saturation, Epworth sleepiness scale, functional outcomes and improvement in the percentage of sleep time with oxygen saturation less than 90%. The study showed a decrease in AHI by 68% ($p<0.001$), ODI decreased by 70% and resulted in an improved quality of life. Importantly in this study, in the group who responded to therapy, the therapy was withdrawn for one week that showed a return of subjective and objective parameters towards the baseline. Institution of the therapy again showed an improvement in the parameters. In addition, adverse effects were found to be very low (2%). The device, 'Inspire', has a stimulation electrode which is placed on the hypoglossal nerve and recruits tongue protrusion function. The sensing lead is placed between the internal and external intercostal muscles to detect an inspiratory effort. The neuro-stimulator is implanted in the mid infra clavicular region on the same side. The device is activated with and controlled by a remote to initiate and terminate the therapy every night in addition to another remote in the control of the physician for device settings. The reduction of sleepiness and improvement in quality of life measures after 12 months use was similar to that of CPAP (16).

Oro- facial exercises: Study by Guimarzaes et al[81] found that some orofacial exercises drawn from speech therapy, targeting the tongue, palate and lateral pharyngeal walls show a response though small. About 67% of patients were found to have a down grading of their OSA. The benefit in the group was more evident in REM sleep. The study in which patients with an average AHI of 15-30 and a BMI< 40 were randomizedto 3-5 sittings of 30 minutes exercise or sham treatment with nasal breathing and irrigations for 3 months demonstrated a reduction in AHI's and could have a role in mild disease.

It was also observed that OSA was lower in those playing oral reed instruments. Didgeridoo is an aboriginal Australian wind instrument which requires continuously vibrating the lips with circular breathing.

(inhaling through nose, expelling air through mouth with cheeks and tongue) A RCT study was designed after a German instructor noted improvement in snoring, daytime sleepiness in some students among didgeridoo players. Study was divided between an observation and active group (20 mins/day for 5 days/week over 4 months). It was found that those with high AHI at baseline showed a greater decrease in AHI in didgeridoo group. A larger study would be helpful to determine the clinical application of the observation[82].

Surgical methods and procedures that modify the anatomical (soft tissue) architecture : This modality for the treatment of OSA is rapidly developing and is an area which holds strong promise. Minimally invasive surgeries such as palatal implants and radiofrequency or laser-assisted uvulopalatopharyngoplasty(UPPP) are not efficacious in adult OSA and may be considered for primary snoring[83]. Many adults do not respond to single operative interven-tions and benefit from planned multilevel upper airway surgical modification either simultaneously or in staged protocols[84,85].

Soft Lasers: Newer soft laser devices have been developed and have been used in East European countries. The results after scheduled number of sittings show improvement in snoring and AHI, though requires confirmation is larger trials[86].

Tongue implants: Surgical interventions include tongue implants (Aspine) consisting of bioabsorbable polymer coils interspersed with silicone elastomers. These are sutured in place through the distal polyester fabric anchors on the mandible at the origin of tongue and the other end being sutured to the body of the tongue to prevent its falling back in sleep. Studies in the US and Europe showed a decrease in the AHI and improvement in ESS[87,88]. The device, however, suffers from a high malfunction rate.

Magnetic implants: Similar to the spring like implants, animal experiments of magnetic implants placed in the tongue base and the postero lateral pharynx that are oriented to repel, producing a force similar to 10-12 cm CPAP. A decrease in the Pcrit was noted in the animals[89].

Midline glossectomy: It is seen that obesity is linked to tongue size, usually due to the deposition of fat in the tongue[90]. There is a correlation between percent tongue fat with BMI. Midline glossectomy has been tried to decrease the volume of the tongue. However, obesity has been found to be associated with poor outcomes with response to surgery being less than 50 %[91].

SMILE: Sub mucosal minimally invasive lingual excision of tongue tissue using ablation through an anterior incision has been studied. The procedure is not approved for patient care but studies comparing this procedure with radio frequency base reduction found no differences in the change of AHI, snoring and ESS[92,93].

Hyoid suspension is also used for OSA treatment as pharyngeal soft tissues attach to the hyoid bone which is not fixed to any bony structure and therefore mobile. The hyoid is advanced to limit its mobility by sutures of fascia-lata superiorly to the inferior border of the mandible and inferiorly to the superior border of the thyroid cartilage[94].

Submucosal linguloplasty is also a procedure that has been used for the treatment of OSA. This procedure too has not received approval for clinical use[95]. The procedure is often combined with palatal surgery like UPPP. Studies have found a reasonable reduction in AHI(44.0 to 12.5: >50% reduction) with improvement in saturation and ESS scores[96].

Robotic assisted surgery using the Da Vinci robotic machine has been found to produce better results[97] than SMILE and RFBOT (radio frequency base of tongue reduction) methods, though they fall short of statistical significance[98].

Maxillo mandibular advancement: Mandibular advancement (MMA) increases the size of the upper airway space and decreases extraluminal tissue pressure. MMA involves correction of an abnormally small upper airway space caused by a small bony enclosure by surgically repositioning both the upper and lower jaws forward thus reducing the likelihood of upper airway collapse[83]. MMA is thought to be the most effective surgical treatment for OSA but is often used after other options have been exhausted due to the long recovery time and potential risks of the surgery. MMA is only effective in carefully selected patients with a particular facial phenotype[99] and those without significant co-morbidities that may impact surgical risk.

Computerized surgical planning: A study involving quantitative computer-assisted videoendoscopy (validated with upper airway magnetic resonance imaging) was performed in 49 (43 males, 6 females) patients with OSA and 39 (22 males, 17 females) controls (apnea hypopnea index [AHI] < 5). Absolute cross-sectional areas and transverse and longitudinal diameters at the retropalatal and retrolingual levels were measured during end of quiet respiration and during Mueller's maneuver in the erect and supine positions, allowing to study static and dynamic morphology (collapsibility) of the upper airway. Upper airway Mueller's studies are predictive and useful (independent samples t test/Mann-Whitney *U* test, ROC) in identifying patients with OSA. These anatomic-site specific OSA predictors/formulas could be used to assist surgeons with quantitative clinical diagnosis, assessment, surgical planning, and outcome assessment tools for OSA patients[100]. Detailed cephalometric analysis conducted on lateral x-rays and using CT & MR for soft tissue is also useful when used with head and neck examination, polysomnographic and endoscopic studies to evaluate OSA patients, and to assist with the planning/ surgical treatment for improvement of upper airway patency[101].

Developments in technology have revolutionized OSA. The current trend is in computer-aided maxillofacial surgery. Cone-beam computed tomography (CBCT), stereophotography, surgical planning software, and intraoperative navigation are the most commonly applied tools. Stereophotography produces 3D facial photographs with natural color and texture, whereas CBCT generates excellent hard-tissue images with a substantially lower radiation than conventional CT scans. Information gathered from CBCT and stereophotography can be used for accurate diagnosis, virtual planning, and simulation of surgery with the aid of specialized softwares. The preplanned treatment can be executed accurately via intraoperative surgical navigation allowing much improved results of surgery[102].

Alexo stent: This is a patented device, consisting of a self-expanding nitinol stent which is inserted by the patient using a special introducer and removed in the morning. It is positioned at the soft palate and prevents collapse of the soft tissue in the velopharynx during sleep that has been confirmed by propofol induced video endoscopies[103]. Study using the device shows a moderate decrease in the AHIs with correction of obstructive apneas and correction of apnea induced oxygen desaturation. The device though was not as effective as CPAP[104].

Velomount: is a proprietary device for the treatment of OSA. It is a malleable wired device which hinges on to the uvula and prevents its fall back in sleep. It has been found to reduce snoring, sleepiness and AHI. A study with the device found a compliance of 40%. Not all subjects can tolerate the device. If tolerated it was seen to have a good compliance and is useful in patients of mild snoring[105]. The main difficulty is to ensure proper fitting of the device. It is not useful in patients with retroglossal obstruction. It has been found to be useful in patients with failed UPPP. However, the scarce data do not support the use of the Velumount as an alternative therapy to CPAP.

Role of drug therapy in the treatment of OSA: A Cochrane review was undertaken in 2013 that looked at the role of drug therapy for OSA in adults. A total of thirty studies over 30 years were assessed for the effect of 25 drugs in the pharmacological treatment for OSA. Primary outcomes for the systematic review were the apnoea hyperpnoea index (AHI) and the level of sleepiness associated with OSA, estimated by the Epworth Sleepiness Scale (ESS). AHI was reported in 25 studies and of these 10 showed statistically significant reductions in AHI and in four altered symptoms of sleepiness. In most people changes were only modest. The authors concluded that "There is insufficient evidence to recommend the use of drug therapy in the treatment of OSA"[106].

These trials evaluating the role of oral drugs for treating OSA have focused on five strategies, ie, increasing ventilatory drive (eg, progestagens, theophylline, acetazolamide), increasing upper airway tone (eg, serotinergics, cholinergics), decreasing rapid eye movement sleep (eg, antidepressants, clonidine), increasing arousal threshold (eg, eszopiclone), and/or increasing the cross-sectional area or reducing the surface tension of the upper airway through topical therapy (eg, fluticasone, lubricant[106]).

Few other drugs show promise of finding practical use. Among them is Dronabinol, which is a non selective cannabinoid type 1 (CB1) and type 2 (CB2) receptor agonist used to treat anorexia/ cachexia of acquired human immunodeficiency syndrome or nausea and vomiting after chemotherapy. This drug improved subjective sleepiness in a study on 17 adults with moderate OSA, without any changes in oxygen saturation index, sleep efficiency and arousal index[107]. Further studies show the drug to shift the sleep to a lower frequency with improved cycling and decreased respiratory rates in all stages, suggesting improved alertness. There is also a decrease in respiratory rate in all stages of sleep[108,109], suggesting an inhibition of vagal activity. This is substantiated further by studies which show phasic activation of the genioglossus[110]. This drug in usual doses does not result in serious side effects.

Role of drugs which have an effect on the loop gain also show promise[111]. Patients with OSA are proven to have unstable ventilatory system resulting in recurrent obstructive events[33,112], due to enhanced loop gain responses. An unblinded study with 500 mg acetazolamide taken twice a day, showed significant suppression of loop gain, thereby decreasing the ventilatory response to arousal[113]. Unfortunately, due to the side effects of prolonged use of acetazolamide its clinical use in OSA is uncertain.

There is evidence of a strong link between gastroesophageal reflux and OSA, and there is a suggestion that treatment of gastro esophageal reflux would decrease AHI and excessive day time sleepiness [114,115]. Subsequent study on the effect of proton pump inhibitors on patients of GERD with associated OSA, showed that about half of OSA episodes were preceded by GE reflux[116]. Use of PPIs (lansoprazole) on a regular basis decreased the numbers of AHI. The drug, however, did not show any change in the level of desaturations during sleep or sleep efficiency. PPIs are used on a routine basis and in general have a high safety level.

Another role of drug therapy is the use of using sedative agents that do not impair upper airway muscle activity but increase the arousal threshold[117,118]. Eszopliclone, has been tested for effects on arousal threshold and OSA severity. In a study it was seen that eszopliclone was associated with an overall increase in the arousal threshold and reduction in AHI associated (23%) with increased sleep duration and quality.

It has been seen that upper airway lining liquid has a higher surface tension in OSA patients compared to healthy controls[119]. Reducing surface tension using an exogenous surfactant improves upper airway patency[120] and improve the closing pressures by almost 2 cm H2O with a reduction of AHI by 20-40%[120,121,122].

Fluid retaining states like heart and renal failure leads to nocturnal fluid shifts[123]. Therefore, measures such as increased activity, compression stockings and diuretic therapy resulting in upto 15% reduction in AHI's[124,125,126].

Acupuncture: is believed to release 5 HT, endorphins and to suppress inflammation[127]. A randomized trial comparing acupuncture to sham acupuncture over a 10 week period showed a statistically significant improvement in the AHI[127]. In another study comparing manual acupuncture to low frequency electro acupuncture (2 hz) that activates more somatic afferents than high frequency EA (10-20 hz) electro acupuncture, showed manual and low frequency acupuncture to have statistically significant effect on the AHI[128].

Multimodality therapy: Based on the observations by Eckart and Sutherland[33,35] use of a multimodality treatment based on the pathophysiology should produce better results in the treatment of OSA. Therefore, in a patient with upper airway anatomy/collapsibility issues- dental appliances, upper airway surgery and possibly oral pressure device (Winx TM), could be useful. In patients with changes in the upper airway response, there are currently no methods to influence pharyngeal dilator muscle activity in the wake state or in sleep. Besides the effort to look at the role of drugs, stimulation of the genioglossus by hypoglossal nerve stimulation could be an option. In those with issues related to arousal threshold to a respiratory stimulus, hypnotics such as eszopiclone and trazadone could be tried. In subjects with problems related to loop gain (ventilator control instability), oxygen and acetazolamide have been found to lower loop gain and may find a place. Therefore, a single agent or a combination of modalities could be used theoretically for the treatment of OSA, based on the physiological phenotyping.

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