Review Article

Obstructive Sleep Apnoea: A Systematic Review of Advances in the Last 1 Year

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ABSTRACT

Obstructive sleep apnoea (OSA) is one of the most common chronic diseases in the world. It has adverse impact on neuro-cognitive, metabolic, cardio-vascular and cerebro-vascular functions. We have reviewed articles from July 2023 till July 2024 from the databases of MEDLINE, EMBASE and Cochrane library using the key words "OBSTRUCTIVE SLEEP APNOEA", "OSA" and "SLEEP DISORDERED BREATHING". A recent meta-analysis done revealed a prevalence of OSA of 54% in general population1. Another meta-analysis revealed a prevalence of 35.9% in older adults with highest prevalence in Asian population which was 37%2. OSA was significantly associated with increasing age, BMI, diabetes mellitus and cardio-vascular disease. PAP therapy continues to be the gold standard of treatment in OSA. The evidence in favour of newer modalities of treatment like HGN, minimally invasive surgeries is increasing with time.

Keywords: Obstructive sleep apnoea, literature review, biomarkers, positive airway pressure therapy.

INTRODUCTION

Obstructive sleep apnoea (OSA) is one of the most common chronic diseases in the world[1-6]. The disease has wide health consequences impacting all major systems of the body[7-13]. It has adverse impact on neuro-cognitive, metabolic, cardio-vascular and cerebro-vascular functions[7-14]. It reduces productivity, affects quality of life, and is associated with increased accident rates[7-14]. Due to its multisystem impact, worldwide distribution and enormous economic costs, there has been an exponential increase in the published literate on OSA in the recent years. Rapid advances in the field of OSA have occurred in the recent past which makes it difficult to track and extract clinically relevant information. The concepts of epidemiology and patho-physiology are rapidly changing and so is the diagnostic and therapeutic approach to these patients. We therefore intended to review the recent literature and segregate articles published in the recent past which carried new evocative information that have changed our understanding of the disease and altered our diagnostic and therapeutic approach to patients with OSA.

Literature search

We reviewed articles from July 2023 till July 2024 from the databases of *MEDLINE*, *EMBASE* and *Cochrane* library using the key words "*OBSTRUCTIVE SLEEP APNOEA*", "*OSA*" and "*SLEEP DISORDERED BREATHING*". The Bibliography of the retrieved articles was also used to find other relevant citations in the recent past. The articles were screened by one specialist each of pulmonary medicine, internal medicine and otorhinolaryngeology with at least 10 years of experience in patients with OSA. A total of 482 relevant articles were retrieved. This comprised of 129 clinical trials, 31 meta-analysis, 103 randomised controlled trials and 219 systematic reviews. The articles were segregated into relevant groups of epidemiology, patho-physiology and treatment.

Answers in Epidemiology

The prevalence of OSA in general population has always been a matter of speculations. There is a huge disparity and heterogeneity in the various population based studies which is due to differences in diagnostic criteria as well as the population studies[1-6]. However recent literature has shed light on many aspects of this question.

A recent meta-analysis done revealed a prevalence of OSA of 54% in general population[1]. Another meta-analysis revealed a prevalence of 35.9% in older adults with highest prevalence in Asian population which was 37%[2]. OSA was significantly associated with increasing age, BMI, diabetes mellitus and cardio-vascular disease[2]. Another systematic review revealed a pooled prevalence of 16% in young adults between 18 and 30 years of age[3]. Another systematic review showed that the prevalence of OSA in pre-school children was 12.8 to 20%4. The review also showed that the prevalence of OSA in this age-group has actually increased over the past decade. Among Indian population a recent meta-analysis done showed a pooled prevalence of 11% in Indian population more in males (13%) than in females (5%)[5].

Similarly, studies done in certain populations with specific diseases like heart failure[6], Parkinsonism[7], idiopathic pulmonary fibrosis[8], sickle cell anaemia[9], primary aldosteronism [10] and floppy eyelid syndrome[11] have revealed a very high prevalence of OSA in these diseases (Table 1).

Table 1: Recent studies evaluating the prevalence of OSA in various chronic diseases

Author and year of publication	Disease	Type of study	OSA Prevalence
Prechaporn W *et al* 2024	Heart failure [6]	Meta-analysis	38.4 %
Maggi G *et al* 2024	Parkinsonism[7]	Meta – analysis	45 %
Wei CR *et al* 2024	Idiopathic pulmonary fibrosis[8]	Meta – analysis	70 %
Taherifard E *et al* 2023	Sickle cell anaemia[9]	Meta - analysis	43 %
Zhang R *et al* 2024	Primary aldosteronism[10]	Meta - analysis	46 %
Bulloch G *et al* 2023	Floppy eyelid syndrome[11]	Meta - analysis	57.1 %

Table 2: Recent studies evaluating new biomarkers in OSA

Author and year of publication	Biomarker	Remarks
Di Lorenzo B *et al* 2024	Platelet distribution volume[22]	OSA more than controls
Di Lorenzo B *et al* 2024	Mean platelet volume[22]	• Increases with OSA severity • Risk factor for CVD
Behnoush AH *et al* 2023	Composite lipid indices[23]	Include visceral adiposity index (VAI), atherogenic index of plasma (AIP) & lipid accumulation product (LAP)
Behnoush AH *et al* 2024	Triglyceride-glucose index[24]	Good diagnostic & prognostic Value
Khalaji A *et al* 2023	Galectin-3[25]	• Good diagnostic & prognostic value • CPAP decreases levels
Behnoush AH *et al* 2023	Endocan[26]	• Endothelial cell damage marker • Good diagnostic & prognostic value

These new studies show the enormity of the disease burden. Given the wide multi-system impact of OSA and such high prevalence, a very low threshold for screening and treatment of OSA should be therefore be kept. Due to very high prevalence of OSA in population-based studies, the role of diagnostic questionnaires like Epworth sleepiness scale [12], Berlin questionnaire[13] and STOPBANG score [14] is expected to diminish in the coming days.

Phenotyping and endotyping of OSA

OSA is regarded as a disorder with wide aetiolgy, varied patho-physiology and diverse response to treatment among different patients. "*Phenotyping*" of OSA into homogenous clusters with similar clinical features and response to treatment is already under development and evolving with time[15]. However, the ultimate goal of phenotyping a disease is to find "*endotypes*" with known patho-physiology, clinical features and treatment response where tailored and individualised management can be offered to all patients.

Widening aetiology

Recently, a meta-analysis investigating the role of air pollution in aetiology of OSA was published[16]. The study revealed heterogeneity in the published literature with many studies finding a relationship between air pollution exposure and AHI[16]. There was increased risk (pooled odds ratio = 1.09) of developing OSA with significant NO_2 exposures, though not statistically significant[16]. The study highlights the need for more investigation into the differential role of air pollutants in the development of OSA[16].

Re-defining Clinical features for diagnosis

OSA is a heterogeneous disease with tremendous variation in the clinical presentation of the patients[15]. Patients may be excessively sleep or have insomnia[17]. They may have no sleep related symptoms at all[15]. A recent meta-anlaysis studying the relationship between OSA and headache revealed a pooled prevalence of headache of 33% in patients with OSA[18]. Males and females with OSA had morning headaches with similar frequency. However, OSA was not found to increase the risk of OSA[18]. Morning headache was the most common type with 33% prevalence followed by sleep apnoea headache which was seen in 25% of the patients.

Rapidly developing diagnostics

Diagnosing OSA with overnight polysomonography (PSG), although a gold-standard test, has its own issues. The problems include availability and cost of overnight PSGs, lack of trained manpower, long waiting periods and work loss due to need for admission[19]. These issues are relevant to both developed as well as the developing world. Newer diagnostic modalities are rapidly developing to address these lacunae. However, the evidence in favour of these new diagnostic modalities especially in terms of usefulness and accuracy is often lacking[19]. A recent systematic review and meta-analysis evaluated the efficacy of recently developed digital diagnostic tools in diagnosing OSA[20]. The

digital tools include smart phone based tools, wearable devices, mattresses, nasal flow devices and other sensors[20]. The digital tools were found to have promising discriminatory power in diagnosing OSA[20]. However, the authors noted that there was lack of good quality studies comparing these newer modalities with the gold standard diagnostic methods[20].

Another meta-analysis found strong correlation between portable sleep study devices and PSG[21]. The authors concluded that portable sleep study devices may become a cost effective and simple way of diagnosing OSA[21]. However, the same was not true for paediatric sleep apnoea where portable sleep study devices were sensitive but not specific for diagnosing OSA[21]. As per the authors, the test may therefore be used for screening along with questionnaires in settings with low availability of overnight PSG[21].

Table 3: Studies evaluating the impact of OSA on cardiovascular and non-cardiovascular health

Author and year of publication	Outcome	Main findings
Prechaporn W *et al* 2024	Heart failure[6]	High prevalence of OSA in HF patients
Ahmed AM *et al* 2023	Resistant hypertension[27]	Increases risk (OR 3.34)
Resende Martinez AB *et al* 2024	Sudden death[28]	Increased risk in those with heart disease
Tong J *et al* 2023	CVS events in ACS[29]	Increased risk of MACE and MACCE
Denis C *et al* 2024	Recovery from CVA[30]	Worse outcome with low O_2 saturation
Xia L *et al* 2023	Diabetese mellitus[31]	- OSA was a risk factor for T2D. - Unidirectional association
Cheong AJY *et al* 2023	Glaucoma[32]	OSA associated with : - higher risk of glaucoma, - More severe ocular findings in glaucoma.
Bartolo K *et al* 2023	Wound healing[33]	- OSA delays wound healing. - Weak evidence
Wu D *et al* 2023	Cancers[34]	OSA may increase risk (OR 1.41)
El Hage Chehade N *et al* 2023	GERD[35]	- OSA increases risk (OR 1.53) - Unidirectional association.
Kasemsuk N *et al* 2023	SN hearing loss[36]	• Increased risk of SNHL • OR Mid frequency = 1.52 • OR High frequency = 1.19
Yeo BSY *et al* 2023	Alzheimer's disease[37]	OSA increases biomarkers
Wang XY *et al* 2023	Bone mass[38]	OSA increases risk of osteoporosis - Male (OR = 2.03) - female (OR = 2.56
Mashaqi S *et al* 2023	Gut barrier[39]	• Increased risk of GBD • Severity increases with AHI & ODI
Bianchi G *et al* 2023	Oral microbiodata[40]	Altered by OSA
Zhu J et al 2023	Periodontitis[41]	OSA increases risk (OR = 2.34)
Wang H *et al* 2023	Testosterone levels[42]	OSA decrease levels in males
Sanapo L *et al* 2024	Foetal growth[43]	OR 1.28 for small for gestational age

Table 4: Studies showing impact of CPAP on cardiovascular and non-cardiovascular health

Author and year of publication	Outcome	Impact of CPAP
Li F *et al* 2023 and Wang YX *et al* 2023	Atrial fibrillation recurrence[45-46]	Decreased risk
Feng J *et al* 2023	Diastolic dysfunction[51]	CPAP improves E/A ratio
Wu Q *et al* 2023	BNP levels[52]	CPAP does not change levels
Herth J *et al* 2023	DM control[54]	Improves glycaemia control with DR relationship

Liu J *et al* 2024	Met syndrome[55]	CPAP treatment lowers blood pressure, fasting glucose, waist circumference, and triglyceride levels.
García-Sánchez A *et al* 2024	Retinal disease[56]	CPAP slows progression of NPDR in OSA.
Hosseini H *et al* 2023	Total oxidant capacity[58]	CPAP significantly increases TOC
Stilo G *et al* 2023	Erectile dysfunction[57]	CPAP improves sexual performance in OSA
Fu W *et al* 2023	Depressive symptoms[59]	CPAP decreases depressive symptoms
Shah R *et al* 2023	Endothelial Inflammatory markers Statins[60]	Statins restore endothelial protection against complement and reduce its downstream pro-inflammatory effects, suggesting a potential approach to reduce residual cardiovascular risk after CPAP in patients with OSA.

Table 5: Recent studies involving newer non-pharmacological therapies in OSA

Author and year of publication	Modality	Remarks
Gupta A *et al* 2023[82]	Yoga in obese OSA patients	Positive impact
Lins-Filho O *et al* 2024[83]	High - intensity interval training (HIIT)	Positive impact
Saba ES *et al* 2024[84]	Orofacial myofunctional therapy	Positive impact
Soreca I *et al* 2024[85]	Bright light therapy for EDD / depressive symptoms	Positive impact
Sweetman A *et al* 2023[86]	Cognitive BT in COMISA (insomnia component)	Positive impact
Georgoulis M *et al* 2023[87]	Mediterranean lifestyle	Positive impact
Chen TA *et al* 2023[88]	Inspiratory muscle training	Positive impact
Carneiro-Barrera A *et al* 2023[89]	Weight loss in OSA for daily functioning & psychiatric sym. (INTERAPNEA RCT)	Positive impact
Niu Y *et al*[90]	Telemedicine and CPAP compliance in OSA	Positive impact

New Biomarkers

The role of biomarkers is increasing in the management of all diseases including malignancies, autoimmune diseases, cardiovascular disorders and critical illnesses[22-26]. These markers are used in diagnosis, guiding and managing treatments and monitoring progression[22-26]. Similarly, certain biomarkers have received a lot of attention as diagnostic and prognostic markers in OSA in the recent years. These include blood markers (mean platelet volume, platelet distribution volume)[22], lipid indices (visceral adiposcity index, atherogenic index of plasma (AIP)[23], lipid accumulation product[23] and triglyceride glucose index)[24], immune markers like galectin-3[25] and endothelial injury markers like endocan[26]. Although these markers are not utilised routinely at present for diagnostic and therapeutic purposes in OSA, evidence is accumulating for their future role in diagnostic, phenotyping, monitoring and therapeutic purposes. For example, mean platelet volume can be used for segregating patients with OSA who have high risk of cardio-vascular death[22]. (Table 3)

Impact of OSA on cardiovascular health

OSA is one of the most important driving factors of cardiovascular disease in an individual[27-30]. The impact of OSA on cardiovascular system is well known[27-30]. The evidence in favour of adverse impact of OSA is increasing day by day and newer pathways have been elucidated in recent years[27-30]. A recent study has shown patients with heart failure have higher prevalence of OSA[6]. OSA is one of the most common causes of resistant hypertension. A recent meta-analysis has shown an odds ratio of 3.34 in patients with OSA[27]. Another study investigating the role of OSA in sudden heart deaths has revealed an increase in risk of death in patients with pre-existing heart diseases[28]. There was no increase in such risk in patients without heart diseases[28].

Another study showed that OSA increased the risk of major adverse cardiac events (MACE) as well as major adverse cardiac and cerebro-vascular events (MACCE)[29]. OSA has also been shown to worsen outcomes in patients recovering with cerebro-vascular accidents[30] (Table 4).

All these recent studies show severe adverse impact of OSA on cardiovascular system[27-30]. This increase in morbidity as well as mortality due to OSA in patients with cardiac and cerebro-vascular events reflects a need for low threshold for diagnosis and treatment of OSA in such patients. The patients with these conditions should be evaluated for the presence of OSA irrespective of their clinical symptoms.

Impact of OSA on non-cardiovascular health

OSA is known to impact all body systems adversely[31-43]. This evidence is getting more robust day by day and the hitherto unknown adverse impacts of OSA are coming to light[31-43]. A recent meta-analysis has found to increase the risk of

developing type 2 diabetes mellitus[31]. This impact is seen to be unidirectional. Similarly OSA has been seen to be associated with increased risk of developing glaucoma. This again has been seen to be a unidirectional relation[32]. It has also been seen to be associated with more severe ocular findings in glaucoma [32]. OSA decreases wound healing[33]. A recent meta-analysis has shown OSA to increase the risk of cancers with odds ratio of 1.41[34]. Similarly other disease has shown increased risk of GERD[35], sensori-neural hearing loss[36], alzeihmers disease[37], osteoporosis[38], altered gut barrier function[39] and perio-dontitis[40-41]. OSA has also shown to be associated with decreased testosterone levels and lower foetal weight[42-43]. This new evidence emphasizes need for evaluation of OSA as a potential cause for such diseases as well as a need for evaluating OSA patients for these complications (table 5).

Impact of positive airway pressure (PAP) therapy on cardiovascular health

Recent studies have showed that PAP therapy has a positive impact on cardiovascular health[44-52]. This includes decreased risk of AF recurrence[45,46], improved diastolic dysfunction[45-52] and BNP levels in patients with heart failure[45-52].

One of the most important recent developments in the risk stratification of patients with OSA is the recognition of "*hypoxic burden*" as an important parameter reflecting the risk of cardiovascular events in patients with OSA[53]. Hypoxic burden reflects with extent of hypoxia during sleep and is determined by the level of oxygen de-saturation as well as the duration spent in such hypoxic state during the sleep[53]. Patients with OSA with increase in "cumulative oxygen de-saturation" have higher risk of cardiovascular events[53] In this regard a recent meta-analysis has revealed that PAP use in such patients with high hypoxic burden decreases the risk of cardiovascular events[53]. The study also revealed that this reduction in the cardiovascular risk has a dose-response relationship[53].

Impact of PAP therapy on non-cardiovascular health

PAP therapy in patients with metabolic syndrome has been shown to decrease fasting glucose levels, lowers blood pressure, waist circumference, and triglyceride levels[54-55]. The relationship between PAP treatment and glucose control is dose response[54-55]. Other recent studies have shown a positive impact of OSA on retinal disease[56], erectile dysfunction[57], total oxidant capacity[58] and depressive symptoms[59].

Similarly, PAP therapy has been shown to improve GLP1 and statin levels reflecting positive impact on inflammatory and endothelial damage markers[60].

All these studies have reinforced the evidence in favour of positive impact of positive airway pressure therapy in patients with OSA. PAP therapy is the gold standard therapy in treatment of patients with OSA. The patients need to be educated about the impact of this modality in order to improve compliance of the patients.

Developments in OSA treatment

Improving PAP therapy

PAP therapy which is the gold standard of treatment in patients with OSA has its own problems[61-63]. The equipment is costly. There are issues with acceptance as well as compliance[61-63]. Lot of improvement and refining of PAP devices has happened over years to make patients more comfortable and compliant[61-63]. These include use of humidifiers, climate controlling tubes, ramp features, expiratory pressure release, need based pressure of auto-PAP devices and compliance monitoring by the instruments[61-63]. However, the evidence in favour or against these modalities is also accumulating gradually [61-63]. An interesting recent systematic review and meta-analysis analysing the difference between nasal mask and nasal pillows revealed no significant difference between the two modalities[61]. Nasal mask and nasal pillow masks are equal in terms of residual AHI and achieved similar therapeutic PAP pressures[61]. Although the nasal mask was associated with statistically significant increase in PAP therapy adherence the difference was of questionable clinical significance[61].

Another recent meta-analysis revealed that PAP instrument had high chances of mis-detected respiratory events including apnoeas as well as hypopnoeas [62]. The study also revealed differences among different manufacturers of PAP devices in event detection criteria and methods as well as accuracy[62].

Another recent study revealed that fixed and automatic PAP machines are equally effective in decreasing AHI as well as compliance and adherence[63]. There was no difference in the quality of life as well as blood pressure reduction with both the modalities. The two modalities were equally effective across effective PAP therapy pressures.

A recent study revealed that patients with morning chronotypes have better adherence to PAP therapy than patients with intermediate and evening chronotypes[64]. The study shows that patient chronotypes may predict PAP therapy adherence[64].

Another study comparing various non-pharmacological methods in improving CPAP adherence revealed that supportive therapy followed by behavioural therapy was the most effective method [65]. The results also support use of multi-disciplinary methods in improving PAP therapy adherence[65].

Nerve stimulation techniques

Nerve stimulation techniques especially hypoglossal nerve stimulation has emerged as an acceptable alternative therapy for patients with OSA. This procedure is less invasive than other surgeries of the upper airways and has an advantage of being a single time procedure without compliance hassle as compared to PAP instruments. A recent meta-analysis on the efficacy of hypoglossal nerve stimulation in the treatment of OSA revealed AHI reduction in 47%, 72% and 82% to less than <5, <10 and <15 events

per hour [66]. The reported success rate was 80% in 12 months and 72 % at 36 months as per *SHER* criteria[66]. The study also showed that although the positive effects consistently decreased over the first 12 months but remained stable till 36 months. This was true for quality-of-life measures as well as PSG parameters [66].

Another meta-analysis studying 34 publications involving 3785 patients with a mean follow up of 11.8 ± 12.2 months revealed that there was consistent positive impact of hypoglossal nerve stimulation on quality-of-life measures including daytime sleepiness, daytime functioning as well as quality of sleep [67]. These two meta-analyses have consolidated evidence about hypoglossal nerve stimulation as an alternative therapy to positive pressure therapy in patients with OSA[66-67]. However, the low success rate in completely normalising PSG parameters should be considered before offering this treatment.

Advances in Oral appliances

A new oral appliance for treatment of OSA known as "*Ronch AP*" was evaluated in a randomised controlled trial in patients with moderate to severe OSA [68]. The average reduction in AHI was from 35 to 19 events per hour in the interventions group as compared to the control group where there was a modest decrease from 31 to 29 events per hour [68]. The authors concluded that the device is a very effective alternative treatment in patients with moderate to severe OSA not tolerating PAP therapy[68].

Increasing role of surgery & orthodontics

Limited palatal muscle resection involves reducing soft palatal volumes as well as tightening the muscles around it to alleviate the symptoms of OSA in patients with retro-palatine narrowing[69]. A recent meta-analysis involving 4 studies and 119 patients revealed consistent but modest reduction of AHI with limited palatal muscle resection. The authors concluded that limited palatal resection can be an effective surgical intervention for certain patients with OSA[96].

Another meta-analysis involving 12 studies and 1373 patients with OSA undergoing expansion sphincter pharyngeoplasty revealed good results in alleviating upper airway anatomical area and volume as well as consistent improvement in PSG parameters[70]. These results were maintained over 5 years post-surgery.

A meta-analysis involving 4 studies and 82 adults analysing the efficacy of maxilla-mandibular advancement in the management of OSA revealed mean percentage reduction of 79.5% in AHI after surgery, although the evidence was graded as low as per the GRADE system[70].

A meta-analysis involving 6 studies and 848 patients evaluating the effectiveness of minimally invasive single stage multi-level surgery in treatment of OSA was conducted [71]. The study pointed out a success rate of 46% in mild/moderate OSA patients and 18% in severe OSA patients. There was no major complication in any patient[71]. This combined with acceptable results in mild to moderate OSA patients may aid decision making in OSA patients in surgical management[71].

A systematic review, involving 8 studies and 614 patients evaluated comparative efficacy of velo-pharyngeal techniques in surgical management of patients with OSA[72]. The study showed that barbed repositioning pharyngeoplasty was the most effective, preferred and safe surgical procedure in these patients[72]. This was closely followed by expansion sphincter pharyngeoplasty[72]. However, the authors noted that the evidence on these procedures was only modest and further studies involving higher number of patients with strict inclusion criteria may be needed to reach a more informed conclusion[72]. Another systematic review and meta-analysis evaluated the role of mandibular advancement in patients with OSA[73]. The study involved 4 trials and 82 adult patients. The authors reported an average reduction of AHI by 79 % from the baseline, although the level of evidence was low as per the GRADE criteria[72].

Another study evaluating the factors responsible for residual OSA patients enrolled previously for adeno-tonsillectomy for mild to moderate OSA[74]. The study revealed that among the 224 children who underwent adeno-tonsillectomy, black children who were non-obese had a 4.9 times higher risk of having residual OSA after adeno-tonsillectomy.

All these studies on surgical methods of treatment in OSA have revealed positive impact of these surgeries in PSG parameters, quality of life and symptoms of OSA[74]. However, the evidence also suggests that correction of PSG parameters is usually not complete with surgical techniques especially in patients with moderate to severe OSA. There is residual OSA in most of these patients[69-74]. The modalities should therefore be offered to cautiously selected patients after a multi-speciality team evaluation. The high likelihood of residual OSA after surgery and consequent PAP therapy requirement should be communicated to these patients before offering surgical treatment.

New insights in pharmacotherapy

Although there is no approved pharmacotherapy for patients with OSA, recent studies have tried various drugs and combinations targeting different aspects of pathogenesis of OSA. The role of these drugs is expected to increase given the accumulating evidence in favour of these drugs. A recent study evaluated various modalities available for treatment of paediatric OSA and compared them using network meta-analysis. The study evaluated and analysed 17 randomised controlled trials involving 1367 children. It was found that intranasal momotasone furoate in combination with oral monteleukast showed highest efficacy and highest probability of being the most effective therapeutic modality[75].

A recent randomised controlled trial evaluating the role of novel anti-muscarinic agent aroxybutenin and noradrenaline re-uptake inhibitor atomoxetene in patients with OSA was published. Both atomoxetene alone as well

as its combination with aroxybutenin resulted in significant drop in AHI as compared to placebo. However, atomoxetene alone resulted in decrease in total sleep time[76]. The most common side effects of the combinations were insomnia, dry mouth and urinary hesitancy. This is a promising result in the development of pharmacotherapy for patients with OSA[76].

A recent meta-analysis evaluated 4 such RCTs evaluating the impact of addition of anti-muscarinic drugs to nor-epinephrine re-uptake inhibitors in patients with OSA. The study revealed that addition of anti-muscarinic agents to norepinephrine re-uptake inhibitors increases both sleep efficiency as well as prolongs sleep time. There was no significant difference in adverse events. The study demonstrates the advantages of using the combination in patients with OSA[77].

The impact of OSA on the risk of diabetes is long established[79]. However, recently a lot of interest has been generated in the impact of anti-diabetic drugs on OSA. A randomised controlled trial comparing the effect of liraglutide when added to CPAP therapy in patients with diabetes mellitus on regular medical management for diabetes showed that liraglutide group had more reduction in AHI, systolic blood pressure and body mass index and higher lowest oxygen saturation. The addition of liraglutide did not increase any side effects[78]. This therapeutic effect was evaluated at the end of 3 months of treatment with liraglutide.

Another multi-centre randomised controlled trial evaluating the role of Dapagliflozin a sodium glucose co-transporter 2 in patients with heart failure with reduced ejection fraction. The trial involving 107 patients found significant improvement in PSG parameters in dapagliflozin group as compared to the control group[79]. The authors concluded that dapagliflozin is an effective drug in the treatment of heart failure which has a positive impact on concomitant OSA[79]. Another study showed that addition to ertugulifozin another sodium glucose co-transporter 2 inhibitor nearly halved the incidence of OSA in patients with heart failure[80].

A network meta-analysis involving 14 studies and 3085 patients evaluated role and efficacy of wakefulness promoting agents like solriamfetol, armodafinil-modafinil and pitolisant in patients with OSA[81]. The study revealed that these agents were useful in managing excessive daytime sleepiness in patients with OSA with solriamfetol likely superior than others. The authors however also noted that adverse events were common with these agents which may compel discontinuation[81].

Other treatments modalities in OSA

Table 6 shows different recent studies evaluating the role of different modalities in OSA[82-87]. These include yoga[82], high-intensity interval training[83], oro-facial myo-functional therapy [84], bright light therapy[84], cognitive behavioural therapy[86], Mediterranean life-style[87], inspiratory muscle training[88], interdisciplinary weight loss and lifestyle intervention[89] and telemedicine-based follow-up management. Most of these modalities had positive impact on OSA[82-90]. However, the evidence in favour is not strong enough to recommend routine use.

Comparison between different modalities of treatment in OSA

A recent single blind randomised controlled trial involving 79 patients comparing CPAP and mandibular advancement devices for excessive daytime sleepiness, mood, fatigue, sustained attention and quality of life in patients with mild OSA (AHI = 5-15 events per hour). The study revealed that CPAP was superior to MAD in normalising PSG parameters and improving quality of life. The two modalities were similar in alleviating fatigue. Neither of the two modalities improved daytime sleepiness, sustained attention and mood[91].

Another randomised controlled trial comparing heated humidified nasal canula and CPAP in children with medical complexities and OSA. The study revealed that both the modalities were similar in improving PSG parameters and sleep efficiency [92].

Another recent systematic review and meta-analysis was recently published which compared HGN with other alternative surgeries in OSA. The study involved 10 studies and 2209 patients. The salient findings of the study were that patients who underwent HGN had significantly lower AHI post-operatively and were more likely to achieve AHI < 15 and AHI < 10. However, there was no difference in the patients achieving AHI < 5 post-operatively. The authors concluded that HGN was an effective alternative treatment for patients with OSA[93]. However, lack of complete alleviation of PSG abnormalities with residual disease in most of the patients should be kept in mind in all patients who are offered HGN stimulation. PAP therapy with its limitations continues to be the gold standard of treatment in OSA.

CONCLUSIONS

The literature on OSA is fast expanding. It is difficult to keep track of enormous number of articles published for treating physicians and surgeons.

The recent studies have shown a prevalence of OSA in at least 1/3rd of the population. These findings emphasize keeping low threshold for suspecting and diagnosing OSA in all patients especially with cardio-vascular and cerebro-vascular risk factors where treatment of OSA or lack of it can alter the possible outcomes. The evidence in favour of negative impact of untreated OSA and positive impact of OSA treatment especially with PAP therapy on health is becoming increasingly evident. PAP therapy continues to be the gold standard of treatment in OSA. The evidence in favour of newer modalities of treatment like HGN, minimally invasive surgeries is increasing with time. Newer diagnostic modalities like portable wearable devices are being increasingly used for diagnosis. However, the evidence on accuracy of these modalities needs to further

evolve. Biomarkers and pharmaco-therapeutic modalities are also evolving with time. It is expected phenotype based individualised targeted therapy in patients with OSA on the basis of individual characteristics shall be done in the coming times.

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