REVIEW ARTICLE

Co-morbid OSA and Depression- What we know and what we need to know

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Abstract

Airway Centric Orthodontics is a philosophy which trumps everything else in contemporary Orthodontics. The philosophy focuses on practice of clinical orthodontics aimed at achieving ideal jaw relationship, establish normal oral function and performance, optimal proximal and occlusal contact of teeth. The central aspect of function and performance is airway and breathing which in fact is hierarchically the most important function for humans. Ideal health and ideal facial development is dependent on correct tongue posture and nasal breathing. Therefore contemporary protocols be it Preventive, interceptive or corrective orthodontics should factor upper airway improvement in addition to improving smile and facial appearance. Today Orthodontic profession is crucial and integral part of the interdisciplinary team in the management of upper airway sleep disorders, thus well poised to become a part of mainstream health profession. The paper would revisit the decision making process in orthodontics and discuss orthodontic strategies to improve the vital human airway which is essential for good health, longevity, and well-being.

Keywords: Airway, malocclusion, orthodontics

Introduction

Obstructive Sleep Apnea is a chronic sleep disorder with five or more apnea or hyponea per hour of sleep occurring due to collapse of upper airway despite the presence of central ventilatory drive[1]. It is usually a result of obesity or craniofacial malformations. Depression, on the other hand, is a psychiatric disorder of similar lifetime risk (8 to 12% in most populations), multi-factorial origin with strong genetic and environmental predispositions[2]. OSA and depression have considerable overlap in both daytime and night-time symptomatology. Because there is a biological plausibility in the association of the two conditions which we shall delve in this article, chances of drawing spurious associations or prescribing inaccurate treatment are both possible. There have been studies looking into the relationship between the two conditions. In this article, we have summed up available literature to provide insight into the relationship between the two conditions so that clinical implications for sleep physicians, psychiatrists, psychologists and general practitioners can be drawn.

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Epidemiology

OSA has grown into a common health condition by the turn of the last century[3-5]. There has been an exponential growth in obesity all over the globe. As a result of multiple etiological factors, the prevalence of obstructive sleep apnea is also on a rise[6]. Few population-based studies place the prevalence of OSA at 4-7% for men and 2-4% for women[3,4]. An Indian study reports OSA prevalence to be as high as 7.5% in adult urban population[4]. The portion of OSA patients remaining untreated or undertreated is more than half. The age distribution of OSA shows gradual increase in incidence with age, peaking after 60 years of age[3]. Years may pass from the time of symptom onset before a diagnosis of OSA is made in most patients. These patients may suffer from depression over time due to increasing constrains they find in day to day living as well as due to metabolic derangements and other socio-economic factors.

Depression In OSA

An observational study in china (n=1327 OSA patients) showed prevalence of Depression as high as 47% on Symptom Checklist 90 and Self-Rating Depression Scale. The study revealed that depressive status is significantly associated with single status, high AHI i.e. OSA, and low family and social supports among those OSA patients.

In another study of newly diagnosed OSA patients(n=121) screened for Depression , prevalence of 44.6% on Beck Depression Inventory(BDI) score (>10) was seen[7]. Another retrospective study of 100 OSA patients puts the proportion to 19%[8]. This tendency is adequate a reason for sleep specialists to screen for Depression in an otherwise clear-cut OSA case. However, a causal relationship has not been established as further studies have shown that AHI values from sleep studies have not been shown to correlate with BDI scores (for depression)[7]. So, only future studies can clarify whether or not a causal relationship exists in this significant association.

OSA in Depression

The prevalence of OSA in patients of major depressive disorder has been consistently reported to be high. In a recent systematic review for prevalence of OSA among psychiatry patients, data was pooled from 6 clinical studies (n=522) with MDD[9]. A pooled prevalence of OSA of 36.3% (95% CI 19.4 to 57.4, p<0.01) was found. After excluding 2 studies (Carney 2006, Ong 2009) with potential selection bias , the pooled prevalence of OSA among 378 people with MDD was recalculated at 25.2% (95% CI 10.2 to 50.2, Q= 58, p<0.01)[10,11]. This was still higher than that reported for Schizophrenia and BPAD in the same review. In the review, an AHI/RDI >5 was taken as diagnostic for OSA while MDD was diagnosed based on DSM-IV (2000) or ICD-10 (1993), all being standard nomenclature. Increasing age and BMI were associated with OSA more significantly in these MDD patients on pooled analysis in the review.

Possible Mechanisms for Association

Theory of Sleep fragmentation and hypoxia

Beebe and Gozal (2002) came up with a theory that sleep fragmentation and hypoxia during sleep causes disruption of sleep-related restorative effects on the prefrontal cortex. This, in turn may result in 'executive dysfunction,' which refers to the abilities crucial for organization, planning, and adaptation[12]. In addition, a functional magnetic resonance imaging (fMRI) study has shown that OSA is associated with reduced lateral prefrontal activation during working memory tasks[13]. Similarly, functional neuroimaging abnormalities within the prefrontal cortex have also been associated with Major Depressive Disorders[14,15].

The association of sleep fragmentation with depression has been evaluated in a study. This study reported significant increase in major flow limitations and desaturations in 19 depressed patients (compared to control subjects) selected without regard to OSA symptoms[16]. The authors hypothesized that respiratory-related sleep fragmentation of hypoxia-induced prefrontal dysfunction may predispose to mood disorder. But the lack of correlation of parameters of OSA and Depression i.e. AHI and BDI respectively as shown in at few studies argues against a causal relation[7].

Overlapping Symptomatology

Another plausible hypothesis is that symptomatology of OSA and Depression overlap to cause the association. According to ICD-10, Depression is a symptom complex of persistent low mood and other somatic complaints, not attributed to the abuse of psychoactive substances

or to an organic mental disorder, lasting for more than 2 weeks[17]. There is a considerable overlap between the somatic complaints of Depression and OSA. These depression symptoms are listed below in Table 1 comparing with similar symptoms that OSA patients can present with:

Considering the above scenario, patients with OSA syndrome may satisfy many somatic criteria for Depression and vise-versa, hence, an association.

Socio-economic and Metabolic causes

OSA patients may suffer from cognitive and memory decline along with constant daytime sleepiness and fatigue. Metabolic profile of untreated OSA patients show higher than normal prevalence of diabetes, dyslipidemia, hyperuricemia. There is also an increased incidence of hypertension and adverse cardiac events, heart failure and stroke in such patients. With these physical and mental disabilities, obesity with general inactivity, and their financial repercussions, OSA patients are under some psychological stress beyond normalcy. Biochemically, there is a constant rise in inflammatory cytokines like Il-6, TNF-alpha in both OSA and depression[18,19]. This may lead to increased incidence of depression over long term. On the other hand, depression is associated with incident and prevalent weight gain, especially in women[20]. Many patients also gain a significant amount of weight due to use of Tricyclic antidepressants, SSRIs or Anti-psychotics use. These patients can develop OSA while being on treatment. In this context, another hypothesis that - OSA and depression both have independent correlation with obesity (or metabolic syndrome) could explain their mutual correlation without dose-response relationship[21].

Therapeutic Trials on Management of Co-morbid OSA and Depression

Primarily OSA with Depressive Symptoms

There have been some prospective cohort studies and fewer RCTs evaluating role of CPAP on depressive symptoms in OSA patients. A systematic review evaluated 26 of these open labelled studies which showed evidence in favour of improvement in depressive symptoms with adequate PAP therapy[22]. The evidence cannot be considered of high quality or of high effect size because of absence of double-blinded placebo controlled trials. In addition, a significant minority of trials still show no benefit of PAP in terms of depressive symptoms[23-26].

In patients with residual sleepiness despite adequate management of OSA, it is a usual practice among sleep physicians to screen for depression if not done initially followed by behavioural and pharmacological treatment.

Primarily Depression with OSA

Though there is scarcity of studies addressing OSA in common cases of depression, some studies in resistant Depression have addressed OSA. In a study of 118 consecutive treatment resistant depression cases in Turkey, 27% were already diagnosed OSA and 11% more were found to be high risk for OSA[27]. These 38% patients benefitted significantly with treatment for OSA in terms of depressive symptoms. The authors concluded that in cases of Treatment Resistant Depression, especially with BMIe"30 kg/m^2, presence of hypertension, and/or dyslipidemia, OSA should be positively screened for. However, placebo effect cannot be ruled out. Never-the-less, treatment was effective and hazards of OSA were also managed which justifies screening and management for OSA in these subset of depressed patients.

Summary of Evidences

1. There is increased prevalence of OSA in Depressive disorder and vice-versa suggestive of a bidirectional association
2. There exists no dose-response relationship to signify a causal relationship
3. Treating for OSA may improve depressive symptoms significantly in most prospective cohort and pre-post studies but not in sham-controlled trials. This may imply either for a strong placebo effect in depression or hint towards depressive symptoms being a part of OSA itself, primary depression not being associated altogether.

OSA and Depression have a complex etiological and demographical overlap with similar symptomatology. At this point, we know that both the conditions have an association that requires enquiring for the other in presence of one. We do not yet know the exact reason for the significant association. Most likely, it is a multi-factorial association with each of the above hypothesis being applicable in various subsets of patients. It is

therefore necessary to appreciate the bidirectional relationship and be vigilant at both ends in order to quickly diagnose and treat the co-morbidities.

Conclusion

Research Perspective

Studies showing clear treatment benefit in OSA complicated by depression are lacking. Hence, double-blinded studies comparing effects of PAP therapy with placebo versus PAP therapy with anti-depressants in patients of OSA with Comorbid Depression may provide insight into the therapeutic implications of this association. The outcomes to look for in these studies should be time to and extent of restoration of EDS, fatigue and other symptoms, safety outcomes like weight gain, and compliance to treatment. The study should stratify cases of depression based on whether they are[1] primary depression[2], reactive to OSA-induced psycho-social stressors[3], Severe OSA induced excessive sleepiness and cognitive impairment or[4] other stressor induced causes. Only with all this information, we can have a clearer idea into depression complicating OSA.

More studies to look for OSA (with appropriate screening questionnaires followed by Sleep study) in new and treatment resistant patients of depression should be carried out to identify significant predictors of OSA in depressed patients.

Studies should also focus on protocol to identify and manage depression induced residual sleepiness in OSA patients on PAP therapy. Likewise, sham controlled RCTs evaluating PAP therapy on resistant depression cases with mild OSA or flow-limitation will help identify the importance of screening for sleep-disordered breathing in the patient group.

Clinical Management Perspective

An OSA patient with co-morbid depression is unlikely to show resilience to withstand fear of PAP therapy. He/she may soon become non-compliant to PAP therapy. Therefore, a vigilant search for depressive symptoms, arrangement of psychological evaluation followed by watchful waiting in mild cases to counselling / drug therapy based on psychiatry opinion is prudent.

From psychiatry practice point of view, a patient identified with depression only and untreated for OSA may not gain any respite from his fatigue and lack of interest, but rather suffer from side effects of TCAs or SSRIs. Likewise, a previously responding patient of Depression may become resistant to drug treatment after significant weight gain and development of OSA. Therefore, patients with depression and excessive daytime sleepiness or fatigue must be screened with OSA screening questionnaires. Appropriate referrals for sleep study should be made based on the same. Periodic reassessment for OSA is required because of the dynamics of obesity in these cases.

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