Sleep and Functional Illness

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Introduction

Good quality sleep is increasingly recognized as paramount to one's health and well-being. The medical community has evolved its thinking about sleep over the past decades to understand it as a dynamic state that is critically important to an individual's psychological and physiological health. In particular, the specialty of otolaryngology has traveled far in its understanding of sleep medicine as it pertains to the burgeoning field of sleep surgery. Otolaryngologists regularly encounter the two most common sleep disorders, obstructive sleep apnea, and insomnia, in patients who are unable to tolerate positive airway pressure (PAP) treatment and are seeking alternative surgical therapy. Functional illnesses such as chronic fatigue syndrome (CFS) and fibromyalgia (FM), which often include sleep-related complaints among their diagnostic criteria, are similarly common in patients seeking care for sleep disorders such as OSA [1, 2]. The subtleties of these conditions as well as contributions from mood disorders can certainly impact sleep and the otolaryngologist's ability to offer successful treatment with sleep surgery. It is of great relevance to any provider who wishes to treat patients with sleep disorders to understand the complexities and nuances of sleep, which touch many aspects of a person's ability to function optimally during the daytime.

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Sleep and Health: A Psychoneuroimmunologic Perspective

It is helpful to briefly review the ways in which sleep affects one's bodily health in a holistic sense. Sleep can be defined as a reversible state of decreased responsiveness to stimuli within one's environment [3]. Sleep influences two major neurobiological systems, the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), which are responsible for the regulation of both innate and adaptive immunity as well as inflammation [4]. Both sleep deprivation and excessive sleep are related to the ability to fight common infectious processes such as pneumonia and the common cold [5, 6]. In addition, short sleep duration and fragmentation reported by insomniacs are more likely to have higher levels of inflammatory markers such as catecholamines and their metabolites in urine samples than those not reporting these sleep deficits [7]. Dysfunctional sleep may mediate and potentiate inflammation that contributes to hypertension, diabetes, cardiovascular disease, cancer, and increased mortality as well as less well-defined functional illnesses such as CFS and FM. Not only is poor sleep duration associated with physical disease, but the inflammatory state resulting from poor sleep may also play a role in mood disorders such as depression [4]. Prolonged insomnia lasting up to a year has been found to be associated with a 14-fold increased risk for depression in the following year [8]. Depression in turn may provide subtle changes in one's perception of illness that can contribute to the manifestations of common functional illnesses.

Relationship of Sleep to Fatigue

What Is Fatigue?

Fatigue is an exceedingly common complaint experienced by the general population. Nonpathologic fatigue is universally experienced and described as short term (less than 3 months) with an easily identifiable cause, such as an acute febrile illness, endocrine pathology, or recovery from trauma or surgery. In contrast, pathologic fatigue is often associated with chronic illnesses such as cancer, multiple sclerosis and depression and has a longer duration [9]. One study found that chronic fatigue (lasting more than 6 months) was present in 2.7–4.2% of patients in a community-based study in a large US city [10]. In particular, fatigue is a subjective experience that can lead to physiological and psychological impairments including poor strength, tiredness, difficulty concentrating as well as decreased morale and mood [11, 12]. It can be difficult in practice to elucidate fatigue because of its multifactorial nature including physical and psychological factors as well as sociocultural and environmental influences [12]. Excessive fatigue is characteristic of patients presenting with chronic insomnia, which is the most common sleep disorder presenting in the primary health care setting [11]. Primary insomnia, labeled as such when it is not due to another sleep, medical, psychosocial or substance abuse disorder, can be more difficult to treat given the lack of an obvious underlying cause.

Chronic Fatigue Syndrome and Sleep

When addressing fatigue in the context of treatment for sleep disorders, it is helpful for the primary care provider, sleep medicine physician and otolaryngologist to understand chronic fatigue syndrome (CFS). CFS is one of a number of mind–body illnesses that is controversial and not well understood with regard to its etiology [13]. It is widespread with an estimated one to two million Americans suffering from this illness, more commonly women, and poses substantial economic costs related to lost productivity and unemployment in the United States [13, 14]. CFS is defined by at least 6 months of "persistent, relapsing fatigue associated with substantial impairments". In addition, four out of eight additional symptoms must be present for diagnosis, one of which is unrefreshing sleep [13]. Many CFS patients are assessed as having poor sleep hygiene and insomnia and can benefit from sleep-focused treatment including cognitive behavioral therapy for insomnia (CBT-i) and exercise therapy. Sleep hygiene should address the "wired but tired" state of mind in patients with CFS. Sleep scheduling, limiting daytime napping, and wind-down activities at night should be encouraged to improve sleep quality [13].

Relationship of Sleep to Pain

Effect of Pain on Sleep

Whether acute or chronic, pain that is severe enough to negatively affect sleep can have physiological and emotional effects on an individual's health, which can then play into the complex factors affecting coexistent functional illness. From a polysomnographic standpoint, the effect of pain on quality and architecture of sleep is related to increased arousals as well as the decreased duration of slow-wave sleep, the most restful phase of sleep [3]. Overall decreased sleep efficiency is also common in patients with widespread musculoskeletal pain and headaches (HA) [3]. In addition, sleep disturbances related to periodic limb movements have been found more often in patients with chronic pain when compared to controls [15].

FM and Sleep

FM, a functional illness that is similar to CFS with the addition of chronic widespread pain as its primary feature, also presents diagnostic and treatment challenges to both primary care and specialist providers. FM is a common musculoskeletal pain syndrome that was first described per rheumatologic criteria in 1990 [16]. It continues to be controversial, having been described by some as the "medicalization of misery" [17]. Its prevalence is estimated at 2% worldwide, and it is reportedly experienced by three to six million people in the United States [13, 18]. FM is defined by 3 or more months of generalized body pain and tenderness, with many specific tender points described by patients [16]. Debilitation in FM is

multifactorial, characterized not only by pain but also by nonrefreshing sleep, fatigue, functional impairment, low energy, and depression among other symptoms. Sleep disturbances affect more than 90% of patients with FM [18]. Like CFS, FM causes significant economic strain on society and the healthcare system due to lost productivity and healthcare utilization [18].

A number of investigators have examined objective sleep data and found that certain patients with FM have fragmented sleep, decreased slow wave sleep, and low sleep efficiency [18]. With regard to these sleep disturbances, they have traditionally been thought to be a result of sleeplessness caused by chronic pain and depression in FM. On the other hand, sleep dysfunction in itself has been found to result in hyperalgesia and a decreased pain threshold [18, 19]. As a result of such findings, researchers postulate a bidirectional relationship between sleep dysfunction and FM that merits further study given that appropriate, early treatment of sleep disorders such as insomnia and OSA may significantly improve symptoms referable to FM [18]. In addition, careful management of pain symptoms in FM with pharmacology and other modalities such as acupuncture and massage may ameliorate the poor sleep experienced by the majority of FM patients.

Sleep and HA

HA are intrinsically related to sleep in that poor sleep can trigger HA, particularly migraines, while chronic migraines and tension-type HA can certainly cause sleep disturbance [3]. Patients with chronic migraines often also experience insomnia, resulting in complaints related to poor sleep time, sleepiness, and unrefreshing sleep [20]. It is important to recognize the link between poor sleep and HA in functional illness given the overlap of these two complaints in common disorders such as CFS and FM [21, 22]. Interestingly, one study showed that FM comorbidity was present in 36% of patients suffering from primary HA, with high levels of tenderness at trigger points, poor sleep adequacy, and severe fatigue when compared to those without FM [21]. HA was also more frequent in CFS patients, with 84% experiencing migraine HA and 81% tension-type HA, and sleep severity scores were significantly worse compared to healthy controls [22].

Patients often present to a primary care provider, sleep medicine specialist, or otolaryngologist with HA contributing to poor sleep, while in fact those HA may be related to the lack of sleep seen in undiagnosed OSA. Providers should have a low threshold to perform polysomnogram (PSG) in patients with suspected OSA and HA among other complaints. In patients found to have concomitant OSA and HA, effective treatment of OSA with PAP has been shown to improve HA [23]. Despite these promising results, patients with OSA and HA undergoing surgical treatment for sleep apnea should be counseled that while successful surgery may improve HA symptoms, the ongoing relationship of an individual's HA to functional illness, chronic pain, fatigue, medication effects, and other disorders will require continued management in the postoperative period.

Surgical Treatment for OSA in the Context of Functional Illness

As the prevalence of OSA reaches 9–38% in the United States, patients with OSA are increasingly referred to an otolaryngology practice for the consideration of sleep surgery [24]. Despite growing attention to OSA and its impact on an individual's cardiovascular and mental health, quality of life, and motor vehicle safety, this disorder remains undiagnosed in a majority of men and women [25]. One factor leading to underdiagnosis may be related to past diagnostic criteria for OSA which emphasized excessive daytime sleepiness (EDS) to ascertain if OSA was present but did not focus on other common symptoms such as "fatigue," "tiredness," or "lack of energy" [26]. Only recently has the American Academy of Sleep Medicine revised its criteria to include fatigue and insomnia as part of the symptomatology of OSA [27]. In practice, a common and complex phenotype of a patient with OSA presents with multiple and often vague complaints of sleepiness, fatigue, and/or low energy. To complicate matters further, OSA can be comorbid with and potentiate other sleep and health conditions, including functional disorders such as primary insomnia, CFS, and FM [1, 2]. Fatigue and chronic pain in these disorders may worsen sleep fragmentation and hypersomnolence already present in OSA, making it difficult to pinpoint the cause of a patient's complaints as only due to the objective presence of apneas and hypopneas.

To accurately understand sleep disorders in the preoperative setting, the otolaryngologist must obtain a comprehensive history, recognizing the interchangeability of the terms fatigue, tiredness, and sleepiness. It is also important to understand that these complaints can coexist in many pathophysiological states, including OSA, especially when comorbid with conditions such as insomnia and depression [11]. A review of sleep aid medications is important given their effects on sleep stages and possible effects on daytime hypersomnolence (see Table 17.1). The otolaryngologist can utilize simple questionnaires, such as the Insomnia Severity Index, Epworth Sleepiness Scale (ESS), and Functional Outcomes of Sleep Questionnaire to not only recognize the nature and severity of the patient's EDS and fatigue complaints but also to counsel patients on realistic expectations of the benefits of sleep surgery. The practitioner should also probe a patient's history to determine if the presence of a functional illness such as CFS and FM may be contributing to the perception of deficits caused by OSA. Recognition of symptoms that point to diagnosed or undiagnosed functional illness may lead to fruitful consultations with primary care, rheumatology, and/or mental health services to address underlying conditions with a variety of modalities prior to pursuing the irreversible option of surgical treatment for OSA. In addition, patients must be counseled that although EDS may be objectively eliminated after surgical treatment of OSA, residual sleepiness and fatigue can remain and be refractory to treatment.

Chronic pain also remains highly relevant to the otolaryngologist's practice when evaluating patients referred for sleep surgery. Patients with FM and their providers should be cognizant of the relationship between poor sleep quality and the experience of pain and how it affects PAP tolerance. Given the highly reported

Table 17.1 Commonly used sleep aid medications and their effects [28, 29]

Class of medication	Example(s)	Mechanism of action	Comments
Sedative-hypnotics			
Benzodiazepines	Temazepam, triazolam	GABA receptor agonist	Excellent sleep induction, risk of addiction and tolerance, withdrawal effects including REM rebound, respiratory depression
Benzodiazepine-like agents	Zolpidem, eszoplicone	GABA receptor agonist	Excellent efficacy, minimal side effects, low abuse potential
Antihistamines	Diphenhydramine	Histamine-1 receptor antagonist	Varyingly effective, side effects of daytime sleepiness, cognitive impairment
Barbiturates	Methaqualone, glutethimide	GABA receptor agonist	Historical interest, high risk of addiction, tolerance, and overdose
Ethanol	Liquor, wine, beer	GABA receptor agonist	Widely used, chronic use causes tolerance, dependence, and diminished sleep efficiency/quality
Sedating antidepressants			
Tricyclic antidepressants	Amitriptyline, imipramine	Serotonin and norepinephrine reuptake inhibitor	Anticholinergic effects, daytime hangover, danger with overdose
Tetracyclic antidepressants	Mirtazipine	Alpha-2-adrenergic receptor antagonist	Dry mouth, weight gain, constipation
Serotonin antagonist and reuptake inhibitor	Trazodone	Serotonin receptor antagonist	Nausea, vomiting, diarrhea, daytime sleepiness, dizziness
Circadian rhythm synchronizer			
Pineal hormone	Melatonin	Intracellular effect on suprachiasmatic nucleus	Adjusts body's internal clock and sleep-wake cycles, useful for shift-work disorder and jet lag; can cause headaches, dizziness, depression, drowsiness

GABA gamma aminobutyric acid

prevalence of FM, it is possible that patients presenting for treatment of OSA also have comorbid FM. In these cases, the surgeon should thoroughly discuss with the patient how wakefulness from nocturnal pain poses treatment challenges with regard to adherence to patient-initiated surgical treatments such as hypoglossal nerve stimulator (HNS), similar to PAP. Importantly, any patient with chronic pain may also be at risk for opioid abuse which can complicate the post-surgical course. Opioid abuse has been found to increase nocturnal hypoxemia and central sleep apnea, which can hamper the surgeon's success in treating patients referred for obstructive sleep apnea [3, 30]. The important role of poor sleep in potentiating pain and vice versa suggests the need to develop multidisciplinary treatments, including pain management services, to improve sleep quality in this complex patient population. Ideally, pain control should be optimized preoperatively, utilizing pharmacologic treatments such as anti-inflammatory and psychotropic medications as well as alternative treatments such as acupuncture and hypnotherapy [19].

Choice of Sleep Surgery in Patients with Functional Illness

Sleep surgery as a field began in the 1980s in the United States with the introduction of the uvulopalatopharyngoplasty (UPPP) by Fujita [31]. Other static surgical procedures, including expansion pharyngoplasty, hyoid suspension, midline partial glossectomy, and tongue base suspension have been developed over the years with varying levels of success. More recently, dynamic therapies are available to patients, most notably the HNS, which has shown promising results in improving the severity of sleep apnea and sleepiness measures [32]. From the author's experience, it is important to tailor the choice of sleep surgery not only to a patient's anatomy but also to their self-motivation and involvement in their own care. In particular, patients undergoing surgery for OSA with sleep issues related to functional disorders will need thorough, individualized counseling as to the nature of the procedure and how it will affect them postoperatively. For example, an OSA patient with comorbid severe insomnia and/or chronic pain in CFS and FM may have worsened sleep fragmentation and sleep time than a patient with OSA only at baseline. If this patient underwent HNS, they would likely require special attention to device settings tailored to their sleep cycle and habits to prevent poor adherence to HNS. On the other hand, static surgical procedures such as UPPP and hyoid suspension may not provide the same objective surgical success as recent results from HNS [32], but will provide patients with a constant result after healing is complete without the need for nightly activation of a device [33]. Whichever procedure is selected, an open and knowledgeable discussion with the patient should take place, taking into account their individual profile with regard to fatigue, insomnia, pain, and mental health issues.

Residual Sleepiness and Fatigue After Treatment of OSA

Otolaryngologists should understand how residual EDS and fatigue, which are well documented in the PAP literature, may affect the perceived success of surgery for OSA. Residual EDS remains a common problem that has been estimated to occur in 5–55% of those using PAP for OSA, with a prevalence of 10–12% remaining even after excluding poor PAP users [34, 35]. Patients with residual EDS after appropriate treatment of OSA with PAP were found to have impaired daytime functioning, more fatigue, and overall worse health than patients without residual EDS [34]. This subjective sense of a poorer quality of life and sleep is also common in patients with functional illnesses and may be a result of the comorbidity of these conditions with OSA.

When evaluating residual EDS after what is considered successful sleep surgery, it is important to confirm the objective efficacy of surgery by tests such as full night PSG, perhaps with a home sleep test, to optimize patient comfort and sleep time. Residual sleepiness can also be confirmed utilizing a multiple sleep latency test as well as a subjective test such as the ESS. If residual EDS exists after successful surgical treatment, the otolaryngologist may need to refer the patient for a thorough evaluation to rule out other causes of sleepiness, including conditions such as

narcolepsy, mood disorders, multiple sclerosis, and neurologic disorders [34]. Adverse effects of residual sleepiness after seemingly successful surgery for OSA must be addressed with the patient, as these patients may still be at risk for detrimental cardiovascular health outcomes as well as an increased risk for home, work, or traffic accidents [35].

Treatment of EDS and fatigue that persist after objectively successful treatment of OSA is challenging. Prevention by early recognition of patients at risk for persistent sleepiness or fatigue starts by identifying patients with significant insomnia, chronic pain, mental health disorders, and functional illnesses such as CFS or FM before surgery. This can aid in counseling patients as to preoperative pharmacologic and psychosocial interventions that may provide a better chance for subjective success after surgery. For example, patients with comorbid depression and insomnia may benefit from sedating antidepressants such as mirtazapine and trazodone rather than the commonly used classes of serotonin and norepinephrine reuptake inhibitors and activating tricyclic antidepressants which have been shown to impair sleep through dysregulation of rapid eye movement (REM) sleep and onset of restless leg syndrome [36]. Close follow-up as to the effects of these medications with mental health professionals is required as sedating antidepressants can also cause a "hangover effect" of increased daytime somnolence.

Postoperatively, residual EDS and fatigue attributable to insomnia can be treated with sleep aid medications and CBT-i to improve a patient's perception of sleep quality and restfulness. Daytime symptoms of tiredness and low energy can be addressed with pharmacologic therapy. In the United States, wake stimulants such as modafinil have been found to be effective in promoting wakefulness through the ascending arousal pathway beginning in the hypothalamus [34]. Mental health providers can also utilize therapy and psychotropic medications to optimize conditions such as depression, anxiety, and post-traumatic stress that often coexist with functional disorders. Otolaryngologists must consider themselves as part of a team caring for these patients and recruit their colleagues in behavioral health, primary care, pain management, rheumatology, and sleep medicine to provide the best chance for objective and subjective success with surgery for sleep apnea.

Summary

Over the past several decades, the medical community has increasingly recognized that sleep is a complex, dynamic state that is critically important to an individual's psychological and physiological health. Sleep disturbances related to functional illness are widespread throughout the general population; in particular, patients experiencing conditions such as CFS and FM often complain of symptoms such as insomnia, daytime sleepiness, and tiredness. Primary care providers and sleep medicine specialists also commonly encounter patients with OSA and may consider referral to otolaryngology for surgery as treatment options become more extensive and individualized. Referring providers and otolaryngologists must understand how sleep complaints related to functional illnesses may act in concert with OSA when

considering sleep surgery. The best chance for the sleep surgeon to develop a productive relationship with a patient and provide relief for their symptoms resides with a careful history that allows for accurate preoperative assessment of functional illness symptoms and realistic expectations for postoperative outcomes with regard to sleepiness and fatigue. Most importantly, the otolaryngologist must function as part of a multidisciplinary team to ensure that patients' functional illnesses are appropriately managed to optimize decision making for surgery and postoperative surgical success.

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