

Sleep Dysfunction and its Association to Chronic Rhinosinuitis: Updated Review

Quinn Orb, MD; Richard R. Orlandi, MD; Jeremiah A. Alt, MD, PhD

Background: Poor sleep has significant effects on health contributing to increased morbidity and mortality. The direct and indirect costs of sleep dysfunction total well in to the billions of dollars annually in the United States. Chronic rhinosinuitis (CRS) affects up to 16% of the US population and has been linked to poor sleep quality with up to three quarters of patients with CRS reporting poor sleep quality. There is a growing body of literature evaluating the relationship between sleep and CRS. In this review, we organize and present the current knowledge on the associations between sleep and CRS as well as identify areas for further investigation.

Data sources: A structured literature search from 1946 to 2016 was conducted in the English language using OVID MEDLINE database, PubMed, and EMBASE.

Review methods: Abstracts were reviewed for relevance and appropriate studies were included in the narrative review.

Results: Studies were analyzed and discussed as they pertained to the following categories of CRS and sleep: (1) subjective measures of sleep dysfunction, (2) objective measures of sleep dysfunction, and (3) outcomes on sleep quality following treatment of CRS. Articles on the pathophysiology of sleep dysfunction in CRS were separately reviewed.

Conclusions: An evolving body of research demonstrates that quality of sleep is compromised in the majority of patients with CRS. Following treatment of CRS, there is significant improvement in subjective sleep quality, but additional research investigating objective measures following treatment is still needed. Additionally, further investigation is required to better elucidate the underlying pathophysiology of the relationship between sleep dysfunction and CRS.

Key Words: Nasal obstruction, sleep quality, quality of life, chronic rhinosinuitis, sleep dysfunction.

Level of Evidence: N/A.

INTRODUCTION

Sleep is vital for overall health, wellness, and emotional well-being.¹ Deficient sleep negatively effects daily performance, quality of life (QOL), and mood.¹ In addition, sleep dysfunction contributes to long-term health consequences, including but not limited to, diabetes, cardiovascular disease, kidney disease, obesity, stroke, depression, and increased mortality.²⁻⁴

Recent investigations have demonstrated that patients with chronic rhinosinuitis (CRS) suffer from

poor sleep quality (SQ) at significantly higher rates than the general population.⁵⁻¹² Chronic rhinosinuitis ranks in the top 10 diagnoses associated with lost productivity for US businesses, and thus has a significant economic impact through both direct and indirect costs.¹³ Treatment of CRS results in improvements in SQ and generally consists of either medical management alone or surgery combined with continued post-operative medical management.¹⁴⁻¹⁸ Furthermore, poor sleep appears to be driving treatment selection as patients with CRS reporting worse sleep dysfunction are more likely to opt for endoscopic sinus surgery (ESS) with continued medical management post-operatively.^{19,20}

Currently, little is understood regarding the etiology and pathophysiology of sleep dysfunction in patients with CRS. The mechanism is likely multifactorial with multiple hypotheses present in the literature including but not limited to rhinologic symptoms such as rhinorrhea, facial pain and/or pressure, and nasal obstruction resulting in reduced sleep. Others have posited that the chronic inflammatory component of CRS is driving reduced sleep through induced brain-immune signaling. This review aims to organize and present the current literature on the role of CRS in sleep dysfunction in order to highlight recent advances and identify further avenues of investigation.

MATERIALS AND METHODS

We performed a comprehensive review of the literature through queries of the OVID MEDLINE database, PubMed,

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

From the Division of Head and Neck Surgery, Rhinology-Sinus & Skull Base Surgery Program, Department of Surgery, University of Utah, Salt Lake City, Utah, U.S.A.

Editor's Note: This Manuscript was accepted for publication 16 November 2016.

Financial Disclosures: Dr. Jeremiah Alt is supported by a grant from the University of Utah Program in Personalized Health and the National Center for Advancing Translational Sciences of the National Institute of Health under Award Number KL2TR001065. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health. Dr. Alt is a consultant for Spirox. Drs. Alt and Orlandi are both consultants for Medtronic. Dr. Orlandi is a consultant for Intersect, 480 Biomedical, and BioInspire.

Conflict of Interest: None

Send correspondence to Jeremiah A. Alt, MD, PhD, 50 N Medical Drive 3C120, Salt Lake City, UT 84132. E-mail: jeremiah.alt@hsc.utah.edu

DOI: 10.1002/liv.2.60

TABLE 1.
Evidence table of studies using subjective validated questionnaires to evaluate the relationship between chronic rhinosinusitis and sleep dysfunction

Study	Year	Study Design	Study Groups	Subjective Clinical Measures	Conclusions
Thomas ⁵⁷	2016	Prospective case series	Refractory CRS	NOSE, PSQI, SNOT-22, RSDI	Nasal obstruction has a limited association with CRS-associated decrease in sleep quality
El Rassi ¹⁷	2016	Prospective observational cohort	Refractory CRS undergoing ESS	SNOT-22	Following ESS, patients report significant and sustained improvements in sleep-related symptoms
Alt ¹⁶	2015	Prospective observational cohort	Refractory CRS with comorbid OSA vs. pts w/o OSA undergoing ESS	PSQI, RSDI, SNOT-22	Patients without OSA reported greater improvements in sleep quality while patients with OSA did not.
Rotenberg ¹⁵	2015	Prospective observational cohort	CRSsNP undergoing ESS w/o septoplasty	EpSS, PSQI, SNOT-22, NOSE	Sleep outcomes improved following ESS
Alt ¹⁴	2014	Prospective observational cohort	Refractory CRS undergoing ESS	PSQI, SNOT-22, RSDI, PHQ	72% of pts had poor sleep at baseline. ESS improved PSQI scores, but mean post-operative scores were 7.2 (<5 considered "good" sleep quality)
Alt ⁵	2013	Prospective observational cohort	Refractory CRS	PSQI, RSDI, SNOT-22	Majority of patients with CRS report poor sleep quality, much greater than in the general population

NOSE = Nasal obstruction symptom evaluation; PSQI = Philadelphia sleep quality index; SNOT-22 = sinonasal outcomes test; EpSS = Epworth sleepiness scale; PHQ = Patient health questionnaire; RSDI = rhinosinusitis disability index; ESS = endoscopic sinus surgery; CRS = chronic rhinosinusitis; OSA = obstructive sleep apnea; CRSsNP = chronic rhinosinusitis without nasal polyps.

and EMBASE. The search consisted of the keywords "chronic sinusitis" OR "rhinosinusitis" OR "chronic rhinosinusitis" AND "sleep" OR "sleep disorders" OR "sleep dysfunction" and was limited to the English language. After removing all duplicate articles from the results of each database, abstracts were reviewed for relevance. Those studies investigating sleep and CRS were deemed appropriate for inclusion in this review.

We organized the relevant literature as it pertains to CRS and sleep as follows: (1) subjective measures of sleep dysfunction, (2) objective measures of sleep dysfunction, and (3) outcomes on SQ following treatment of CRS. Articles discussing the pathophysiology of sleep dysfunction were reviewed separately and discussed as they relate to one of two primary hypotheses on the etiology of sleep dysfunction: (1) nasal obstruction or (2) inflammatory cytokines.

RESULTS

After removing duplicate articles from our preliminary search of the three databases, we identified a total of 510 articles. A total of 452 articles were excluded on the basis that the researchers did not specifically investigate the relationship between CRS and sleep. Of the remaining 58 articles, only 8 explicitly evaluated sleep in patients with CRS and were included in the review. These articles were then carefully read, analyzed, and compared for inclusion in this review. The articles were divided into subgroups consisting of studies using subjective validated questionnaires to evaluate SQ (Table 1) and studies using objective clinical measures of sleep (Table 2). Of the

TABLE 2.
Evidence table of studies using objective clinical measures to evaluate the relationship between chronic rhinosinusitis and sleep dysfunction

Study	Year	Study Design	Study Groups	Objective Clinical Measures	Conclusions
Yalamanchali ³⁷	2014	Retrospective case series	CRS with mild, moderate or severe OSA	PS	No significant changes in NREM stage N2, stage N3, and REM sleep following ESS.
Tosun ³⁶	2009	Prospective observational cohort	CRS w nasal polyposis undergoing ESS	PS	No difference in the number of arousals and percentage of time in NREM or REM sleep following ESS.

OSA = obstructive sleep apnea; ESS = endoscopic sinus surgery; VAS = visual analog scale; CRS = chronic rhinosinusitis; ESS = endoscopic sinus surgery; NREM = non-rapid eye movement; REM = rapid eye movement.

TABLE 3.
Evidence table of studies evaluating sleep outcomes following surgical management of CRS

Study	Year	Study Design	Study Groups	Clinical Measures	Conclusions
Rassi ¹⁷	2016	Prospective observational cohort	Refractory CRS undergoing ESS	SNOT-22	Following ESS, patients report significant and sustained improvements in sleep-related symptoms
Alt ¹⁶	2015	Prospective observational cohort	Refractory CRS with comorbid OSA vs. pts w/o OSA undergoing ESS	PSQI, RSDI, SNOT-22	Patients without OSA reported greater improvements in sleep quality while patients with OSA did not.
Rotenberg ¹⁵	2015	Prospective observational cohort	CRSsNP undergoing ESS w/o septoplasty	EpSS, PSQI, SNOT-22, NOSE	ESS improved sleep outcomes
Alt ¹⁴	2014	Prospective observational cohort	Refractory CRS undergoing ESS	PSQI, SNOT-22, RSDI, PHQ	72% of pts had poor sleep at baseline. ESS improved PSQI scores, but mean post-operative scores were 7.2 (<5 considered "good" sleep quality)
Yalamanchali ³⁷	2014	Retrospective case series	CRS with mild, moderate or severe OSA, undergoing ESS and septoplasty	PS	Mild improvement in AHI among patients with moderate and severe comorbid OSA.
Tosun ³⁶	2009	Prospective observational cohort	CRS w nasal polyposis undergoing ESS	PS, VAS, EpSS	Improvement in VAS and EpSS scores, but no change in AHI following ESS.

CRS = chronic rhinosinusitis; SNOT-22 = Sino-Nasal Outcome Test; ESS = endoscopic sinus surgery; OSA = obstructive sleep apnea; PSQI = Pittsburgh Sleep Quality Index; RSDI = Rhinosinusitis Disability Index; EpSS = Epworth Sleepiness Scale; NOSE = Nasal Obstruction Symptom Evaluation; PHQ = Patient Health Questionnaire; PS = Polysomnography; VAS = Visual Analog Scale; CRSsNP = chronic rhinosinusitis without nasal polyposis; AHI = Apnea-hypopnea Index.

8 studies, 6 specifically evaluated the outcomes of surgery on SQ in patients with CRS (Table 3).

In an attempt to better understand and explain the mechanism of sleep dysfunction in CRS, we performed

an additional review of the literature investigating the role of inflammatory cytokines in sleep physiology and the association of these cytokines with CRS. This separate review of the literature is summarized in Table 4.

TABLE 4.
Somnogenic substances and their effects on sleep architecture

Somnogenic Substances	NREMS	REMS	CRS	Reference
IL-1 β	$\uparrow \leftrightarrow \downarrow$	\uparrow	+	Krueger ⁴¹ , Lennard ⁵⁴ , Mullo ⁵⁸ , Schmidt ⁵⁹
IL-1 R1	\downarrow			Opp ^{42,43,60} , Schmidt ⁵⁹
IL-2	\uparrow			Kubota ⁶¹ , Seleznev ⁶²
IL-4	\downarrow		+	Krueger ⁴¹ , Kushikata ⁶³ , Lennard ⁵⁴
IL-8	\uparrow		+	Seleznev ⁶² , Garcia-Garcia ⁶⁴ , Mullo ⁵⁸
IL-6	\downarrow	\downarrow	+	Bauer ⁶⁵ , Vgontzas ⁶⁶ , Hogan ⁶⁷ , Ghaffar ⁵³ , Rothaug ⁶⁸ , Oyanedel ⁶⁹
IL-10	\downarrow		+	Krueger ⁴¹ , Kushikata ⁷⁰ , Opp ⁴³ , Toth ⁷¹ , Jyonouchi ⁷²
IL-13	\downarrow		+	Kubota ⁷³ , al Ghamdi ⁷⁴ , Reh ⁷⁵ , Lennard ⁵⁴
NF- $\kappa\beta$	\uparrow		+	Kubota ⁷³ , Xu ⁷⁶ , Lane ⁷⁷
IL-15	\uparrow			Kubota ⁶¹
IL-18	\uparrow			Kubota ⁶¹ , Okano ⁷⁸
Interferon- α	$\uparrow \leftrightarrow \downarrow$	\downarrow		Bohnet ⁷⁹
Interferon- γ	\uparrow			Kubota ⁸⁰ , Shin ⁸¹
TNF- α	\uparrow		+	Krueger ⁴¹ , Kubota ⁸⁰ , Lennard ⁵⁴
TGF- β	\downarrow			Kubota, Kuo ⁸²
Histamine	\downarrow			Tashiro ⁸³ , Ikeda-Sagara ⁸⁴
CystLT	\uparrow			Okuda ⁸⁵ , Sri-Kantha ⁸⁶ , Perez-Novo ⁸⁷
Toll-Like Receptors 2	\uparrow		+	Sartorius ⁸⁸ , Lane ⁷⁷
Toll-Like Receptors 4	\uparrow		+	Sartorius ⁸⁸ , Lane ⁷⁷ , Lauriello ⁸⁹

interleukin (IL); nuclear factor kappa beta (NF- $\kappa\beta$); tumor necrosis factor (TNF); tissue growth factor (TGF); cysteinyl-leukotriene (CystLT); non-rapid eye movement sleep (NREMS); rapid eye movement sleep (REMS); chronic rhinosinusitis (CRS). " \uparrow ," " \leftrightarrow ," or " \downarrow " indicate mean influence on NREMS or REMS. "+" indicates that the cytokines have been shown to be involved in CRS. All arrows and (+) indicate statistically significant findings.

Mean PSQI Score by Disease

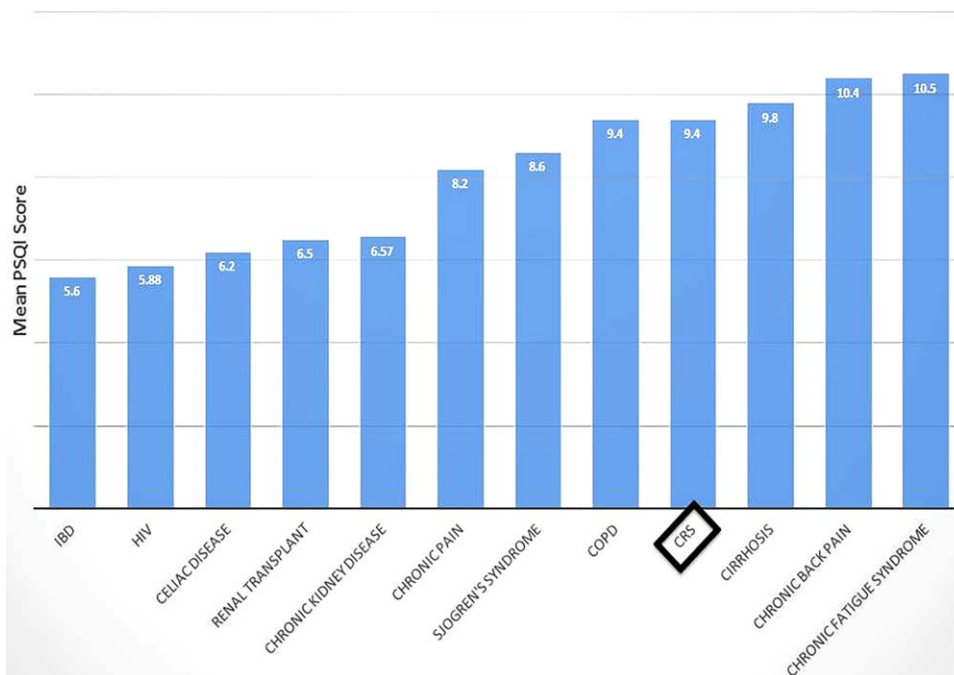


Fig. 1. Comparing mean PSQI scores for diseases associated with poor sleep quality

DISCUSSION

Subjective Measures of Sleep Quality

Over the past 15 years, it has become clear that patients with CRS have an overall reduced QOL as measured by a variety of patient-reported outcome measures (PROMs).²¹ Two well-known PROM instruments for CRS, the sinonasal outcomes test (SNOT-22) and the Rhinosinusitis Disability Index (RSDI), have sleep specific questions or subdomains that have been shown to be associated with overall CRS disease-specific QOL.^{19,22} Despite the importance of SQ in overall patient reported QOL, there have been limited investigations that specifically evaluated the relationship between sleep and CRS. One of the first studies performed by Benninger et al. in 2010 demonstrated that scores pertaining to sleep on the RSDI significantly improved following ESS.²³ These results were again confirmed more recently demonstrating significant improvements in sleep-related symptoms on the SNOT-22 after undergoing ESS for treatment of recalcitrant CRS.¹⁷

To further investigate SQ in patients with CRS, investigators have employed multiple sleep-validated instruments including the Epworth sleepiness scale (EpSS) and the Pittsburgh Sleep Quality Index (PSQI). When compared to other chronic diseases, mean PSQI scores among patients with CRS are near the higher end of the spectrum (Fig. 1). Patients with CRS report overall worse SQ on the PSQI than patients with other chronic diseases such as inflammatory bowel disease, HIV, chronic kidney disease, and Sjogren's Syndrome.²⁴⁻³¹ In fact, only patients with chronic fatigue syndrome, chronic back pain, and cirrhosis reported worse SQ.³²⁻³⁵ There have only been a few studies that

have evaluated PSQI scores before and after treatment of chronic illnesses associated with poor SQ. Figure 2 compares the results of three individual studies that examined mean PSQI scores among patients with either COPD, celiac disease, or CRS at baseline and following treatment.^{14,28,31} Of these three illnesses, CRS was the only disease in which the intervention involved surgical management. The change between pre-treatment and post-treatment scores was the greatest for the CRS patients and was more than two times greater than in COPD and more than three times greater than in celiac disease.

Given the high prevalence of poor SQ among patients with CRS, and the associated health consequences, there has been increasing interest in the sleep-specific outcomes of different treatment modalities used

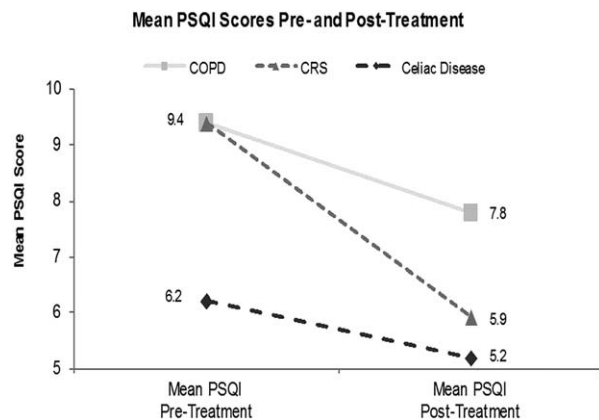


Fig. 2. Comparison of mean PSQI scores in patients before and after treatment of the underlying chronic disease

to manage the disease. Not surprisingly, SQ and general QOL appear to be strongly correlated providing further evidence for the importance of addressing SQ in caring for patients with CRS. Patients with “poor” SQ report significantly worse QOL on CRS-disease specific questionnaires than patients with “good” SQ (a PSQI score <5 suggests “good” SQ while a score >5 represents “poor” SQ). Additionally, patients with poor SQ are more likely to experience comorbid depression.⁵ Multiple prospective studies evaluating sleep outcomes following ESS have demonstrated significant improvements in SQ on both the PSQI and EpSS (Table 3). These improvements strongly correlate with overall enhancement of global QOL scales and persist even after removing SQ specific survey items from QOL questionnaires.¹⁴

Objective Measures of Sleep Quality

Polysomnography (PSG) is the gold standard for objectively measuring SQ. By analyzing sleep architecture including number of arousals and percentage of time in non-rapid eye movement (NREM) or rapid eye movement (REM), PSG provides a more thorough understanding of SQ and the physiology of sleep. Despite the standard practice of employing medical management for the initial treatment of CRS, to our knowledge there have been no studies to date evaluating SQ measures following medical management alone of patients with CRS. Table 2 shows the compiled studies that have evaluated objective measures of SQ in patients with CRS following ESS. In 2009, Tosun et al. studied the effects of ESS on SQ in patients with chronic rhinosinusitis with nasal polyps (CRSwNP). Despite statistically significant improvements in subjective measures such as EpSS scores and visual analog scale ratings of snoring severity, there was no difference in the number of arousals and percentage of time in NREM or REM sleep following ESS.³⁶ More recently, a retrospective study divided CRS patients with comorbid OSA who underwent ESS into three groups: patients with mild OSA, moderate OSA, and severe OSA. Following surgery, patients underwent PSG studies which demonstrated no improvement in objective measures of SQ with no significant changes in NREM stage N2, stage N3, and REM sleep.³⁷

Treatment: Medical vs. Surgical. Typically, the treatment for patients with CRS begins with appropriate medical management. For patients with CRSsNP, saline irrigation, intranasal corticosteroid sprays, and a short course of oral antibiotics are recommended as a minimal initial treatment, with oral corticosteroids as an option. For patients with CRSwNP, saline irrigation, intranasal corticosteroid sprays, and a short course of oral corticosteroids are recommended as a minimal initial treatment, with oral antibiotics as an option.³⁸ When patients do not respond to appropriate medical management, ESS is often considered as the next treatment option.³⁸ Multiple prospective studies evaluating sleep outcomes following ESS demonstrate significant improvements in subjective SQ scores on both the PSQI and EpSS (Table 4).^{14,15,17} However, despite statistically significant improvements following treatment, mean

post-operative PSQI scores continue to remain within a range that is consistent with “poor” SQ (PSQI scores > 5).¹⁴ This suggests that while treatment improves the patient experience, outcomes following ESS are not necessarily clinically significant and patients likely continue to suffer from sleep dysfunction after surgery.

Our group has investigated the SQ outcomes of patients electing either medical or surgical management of CRS using the PSQI. Patients undergoing ESS experienced a significant improvement in PSQI scores while scores among patients undergoing medical management actually worsened following treatment. This suggests that patients with CRS suffering from poor SQ will likely experience greater improvement in sleep dysfunction following surgery than with medical management.³⁹

Etiopathogenesis. While our understanding of sleep dysfunction in CRS remains in its infancy, there is a large body of evidence that suggests that cytokines and their receptors play key roles in sleep physiology in both sickness and health (Table 4). Previous work using animal models has shown that Interleukin (IL)-1 β and tumor necrosis factor (TNF)- α are involved in the physiological regulation of rapid eye movement sleep (REMS) and non-rapid eye movement sleep (NREMS) with both cytokines inducing sleep when administered intracerebroventricularly.⁴⁰⁻⁴⁴ Conversely, cytokines that are upregulated in CRS such as IL-4, IL-13, and TGF- β have been shown to antagonize the effects of IL-1 β and TNF- α and act to decrease sleep.^{45,46} A recent study correlating the cytokine levels from sinonasal tissue of CRS patients with subjective QOL measures found that increased expression of IL-4 and TGF- β was associated with decreased SQ.⁴⁷ Additionally, IL-13 expression was associated with worse CRS specific disease severity scores and worse QOL.⁴⁷ Although many holes exist and further efforts are needed, taken together, these results suggest a plausible association between cytokines implicated in CRS and associated sleep dysfunction among patients with this chronic illness.

Elevated levels of inflammatory cytokines are also thought to play a role in the pathogenesis of depression.⁴⁸ Depression alone is associated with an increased risk of sleep disorders and decreased SQ with an estimated 90% of people with depression experiencing some form of sleep dysfunction.⁴⁹ Additionally, when compared to the general population, CRS patients have a higher prevalence of depression with nearly one-third of patients experiencing depressive symptoms.⁵⁰ Comorbid depression in patients with CRS has been shown to be an independent predictor of poor SQ.⁵ It is likely that comorbid depression related to chronic inflammation in CRS is an additional factor contributing to poor SQ in this unique population of patients.

The relationship between sleep dysfunction, depression, and CRS continues to be poorly understood. It remains unclear if it is the increased prevalence of depression in CRS that is contributing to poor SQ or if chronic inflammation results in poor SQ which in turn worsens depression. Current evidence evaluating the pathophysiology of depression in other chronic diseases, such as chronic pain and chronic GI inflammation,

suggests that there is a component of systemic inflammation that may be contributing to the pathophysiology of comorbid depression in these diseases.^{51,52} Specifically, the cytokines TNF- α , IL-1 β , and IL-6 have all been found to be elevated in patients with chronic inflammatory diseases and comorbid depression.⁵² These same cytokines are also elevated in patients with CRS (Table 4).^{53,54} Thus, it is possible that elevated levels of inflammatory cytokines either locally or systemically may be contributing to the increased prevalence of depression among CRS patients when compared to the general population. Further research is required in this area to better understand the etiology of depression in CRS and its association with sleep dysfunction.

In addition to comorbid depression, patients with CRS commonly suffer from symptoms of facial pain and pressure related to chronic congestion and inflammation of the paranasal sinuses. As mentioned previously, chronic pain has been linked to depression and also contributes to sleep dysfunction.^{52,55,56} Furthermore, CRS patients with pain have been shown to have worse overall disease-specific QOL.⁵⁵ Similar to depression, chronic pain is independently associated with sleep dysfunction.³⁰ As a result, it is likely that facial pain is an additional factor contributing to poor SQ in this unique population of patients.

The pathophysiology of sleep dysfunction in CRS appears to be multifactorial with inflammation, depression, and pain influencing SQ. Thus, it is likely that the increased prevalence of these comorbidities in CRS is contributing to poor SQ among patients with the disease. Additional research into the associations between elevated inflammatory cytokines, depression, and pain in CRS is vital to understanding sleep dysfunction in this population. Further knowledge of this complex interplay has the potential to change treatment paradigms and ultimately contribute to improvement in patient outcomes.

CONCLUSION

There is currently an evolving body of evidence to support the relationship between sleep dysfunction and CRS. Multiple studies have demonstrated that patients with CRS are more likely to suffer from poor SQ when compared to the general population. Furthermore, subjective measures of SQ improve following ESS. However, there remains a limited number of studies evaluating objective SQ outcomes following treatment of CRS. Thus, more research is needed to better understand the effects of medical management alone or ESS plus medical management on objective measures of SQ. While the etiology and pathophysiology of sleep dysfunction in CRS remains unknown, recent studies suggest that the inflammatory phenotype in patients with CRS may be altering sleep physiology. Our understanding of the relationship between CRS and sleep dysfunction remains in its infancy. Further study is needed to evaluate objective outcomes of treatment and investigate the mechanisms contributing to poor SQ among CRS patients. A better understanding of the pathophysiology will enable

clinicians to improve QOL and sleep dysfunction in patients with CRS.

BIBLIOGRAPHY

1. Why is sleep important? [U.S. Department of Health & Human Services: NIH National Heart, Lung, and Blood Institute Web site]. February 22, 2012. Available at: <https://www.nhlbi.nih.gov/health-topics/topics/sdd/why>. Accessed December 4, 2016.
2. Cappuccio FP, Miller MA. Sleep and mortality: cause, consequence, or symptom? *Sleep Med* 2013;14:587–588.
3. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep* 2010;33:585–592.
4. Azevedo Da Silva M, Singh-Manoux A, Shipley MJ, et al. Sleep duration and sleep disturbances partly explain the association between depressive symptoms and cardiovascular mortality: the Whitehall II cohort study. *J Sleep Res* 2014;23:94–97.
5. Alt JA, Smith TL, Mace JC, Soler ZM. Sleep quality and disease severity in patients with chronic rhinosinusitis. *The Laryngoscope* 2013;123:2364–2370.
6. Wells GA, Li T, Kirwan JR, et al. Assessing quality of sleep in patients with rheumatoid arthritis. *J Rheumatol* 2009;36:2077–2086.
7. Ulus Y, Akyol Y, Tander B, Durmus D, Bilgici A, Kuru O. Sleep quality in fibromyalgia and rheumatoid arthritis: associations with pain, fatigue, depression, and disease activity. *Clin Exp Rheumatol* 2011;29:S92–S96.
8. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). *Arthritis Care Res (Hoboken)* 2011;63(Suppl 11):S287–S296.
9. Milross MA, Piper AJ, Norman M, et al. Subjective sleep quality in cystic fibrosis. *Sleep Med* 2002;3:205–212.
10. Merlino G, Fratticci L, Lenchig C, et al. Prevalence of 'poor sleep' among patients with multiple sclerosis: an independent predictor of mental and physical status. *Sleep Med* 2009;10:26–34.
11. Martinez-Lapiscina EH, Erro ME, Ayuso T, Jerico I. Myasthenia gravis: sleep quality, quality of life, and disease severity. *Muscle Nerve* 2012;46:174–180.
12. Jankelowitz L, Reid KJ, Wolfe L, Cullina J, Zee PC, Jain M. Cystic fibrosis patients have poor sleep quality despite normal sleep latency and efficiency. *Chest* 2005;127:1593–1599.
13. Goetzl RZ, Hawkins K, Ozminkowski RJ, Wang S. The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large U.S. employers in 1999. *J Occup Environ Med* 2003;45:5–14.
14. Alt JA, Smith TL, Schlosser RJ, Mace JC, Soler ZM. Sleep and quality of life improvements after endoscopic sinus surgery in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2014;4:693–701.
15. Rotenberg BW, Pang KP. The impact of sinus surgery on sleep outcomes. *Int Forum Allergy Rhinol* 2015;5:329–332.
16. Alt JA, DeConde AS, Mace JC, Steele TO, Orlandi RR, Smith TL. Quality of life in patients with chronic rhinosinusitis and sleep dysfunction undergoing endoscopic sinus surgery: a pilot investigation of comorbid obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg* 2015;141:873–881.
17. El Rassi E, Mace JC, Steele TO, Alt JA, Smith TL. Improvements in sleep-related symptoms after endoscopic sinus surgery in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2016;6:414–422.
18. Kiely JL, Nolan P, McNicholas WT. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. *Thorax* 2004;59:50–55.
19. DeConde AS, Mace JC, Bodner T, et al. SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2014;4:972–979.
20. Orb Q, Mace JC, DeConde AS, et al. Patients electing medical vs surgical treatment: emotional domain of the Rhinosinusitis Disability Index associates with treatment selection. *Int Forum Allergy Rhinol* 2016;6:315–321.
21. Smith TL, Rhee JS, Loehr TA, Burzynski ML, Laud PW, Nattinger AB. Objective testing and quality-of-life evaluation in surgical candidates with chronic rhinosinusitis. *Am J Rhinol* 2003;17:351–356.
22. Benninger MS, Senior BA. The development of the Rhinosinusitis Disability Index. *Arch Otolaryngol Head Neck Surg* 1997;123:1175–1179.
23. Benninger MS, Khalid AN, Benninger RM, Smith TL. Surgery for chronic rhinosinusitis may improve sleep and sexual function. *Laryngoscope* 2010;120:1696–1700.
24. Ranjbaran Z, Keefer L, Farhadi A, Stepanski E, Sedghi S, Keshavarzian A. Impact of sleep disturbances in inflammatory bowel disease. *J Gastroenterol Hepatol* 2007;22:1748–1753.
25. Dabaghzadeh F, Khalili H, Ghaeli P, Alimadadi A. Sleep Quality and its correlates in HIV positive patients who are candidates for initiation of antiretroviral therapy. *Iran J Psychiatry* 2013;8:160–164.
26. Iliescu EA, Yeates KE, Holland DC. Quality of sleep in patients with chronic kidney disease. *Nephrol Dial Transplant* 2004;19:95–99.
27. Priori R, Minniti A, Antonazzo B, Fusconi M, Valesini G, Curcio G. Sleep quality in patients with primary Sjogren's syndrome. *Clin Exp Rheumatol* 2016;34:373–379.

28. Zingone F, Siniscalchi M, Capone P, et al. The quality of sleep in patients with coeliac disease. *Aliment Pharmacol Ther* 2010;32:1031–1036.
29. Pourfarziani V, Taheri S, Sharifi-Bonab MM, Mohammadzadeh M. Assessment of sleep disturbance in renal transplant recipients and associated risk factors. *Saudi J Kidney Dis Transpl* 2010;21:433–437.
30. Meneffee LA, Frank ED, Doghramji K, et al. Self-reported sleep quality and quality of life for individuals with chronic pain conditions. *Clin J Pain* 2000;16:290–297.
31. Lan CC, Huang HC, Yang MC, Lee CH, Huang CY, Wu YK. Pulmonary rehabilitation improves subjective sleep quality in COPD. *Respir Care* 2014;59:1569–1576.
32. Mariman A, Vogelaers D, Hanouille I, Delesie L, Pevernagie D. Subjective sleep quality and daytime sleepiness in a large sample of patients with chronic fatigue syndrome (CFS). *Acta Clin Belg* 2012;67:19–24.
33. Marty M, Rozenberg S, Duplan B, Thomas P, Duquesnoy B, Allaert F. Quality of sleep in patients with chronic low back pain: a case-control study. *Eur Spine J* 2008;17:839–844.
34. Stewart CA, Auger RR, Enders FT, Felmlee-Devine D, Smith GE. The effects of poor sleep quality on cognitive function of patients with cirrhosis. *J Clin Sleep Med* 2014;10:21–26.
35. Marin R, Cyhan T, Miklos W. Sleep disturbance in patients with chronic low back pain. *Am J Phys Med Rehabil* 2006;85:430–435.
36. Tosun F, Kemikli K, Yetkin S, Ozgen F, Durmaz A, Gerek M. Impact of endoscopic sinus surgery on sleep quality in patients with chronic nasal obstruction due to nasal polyposis. *J Craniofac Surg* 2009;20:446–449.
37. Yalamanchali S, Cipta S, Waxman J, Pott T, Joseph N, Friedman M. Effects of endoscopic sinus surgery and nasal surgery in patients with obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2014;151:171–175.
38. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol* 2016;6(Suppl 1):S22–S209.
39. Cox DR, Ashby S, Mace JC, et al. The Pain-Depression Dyad and the association to Sleep Dysfunction in Chronic Rhinosinusitis. *Int Forum Allergy Rhinol* 2016; doi: 10.1002/alar.21843.
40. Fang J, Wang Y, Krueger JM. Effects of interleukin-1 beta on sleep are mediated by the type I receptor. *Am J Physiol* 1998;274:R655–R660.
41. Krueger JM. The role of cytokines in sleep regulation. *Curr Pharm Des* 2008;14:3408–3416.
42. Opp MR, Krueger JM. Interleukin-1 is involved in responses to sleep deprivation in the rabbit. *Brain Res* 1994;639:57–65.
43. Opp MR, Obal F Jr, Krueger JM. Interleukin 1 alters rat sleep: temporal and dose-related effects. *Am J Physiol* 1991;260:R52–R58.
44. Susic V, Totic S. “Recovery” function of sleep: effects of purified human interleukin-1 on the sleep and febrile response of cats. *Metab Brain Dis* 1989;4:73–80.
45. Deleuran B, Iversen L, Deleuran M, et al. Interleukin 13 suppresses cytokine production and stimulates the production of 15-HETE in PBMC. A comparison between IL-4 and IL-13. *Cytokine* 1995;7:319–324.
46. Muzio M, Sironi M, Polentarutti N, Mantovani A, Colotta F. Induction by transforming growth factor-beta 1 of the interleukin-1 receptor antagonist and of its intracellular form in human polymorphonuclear cells. *Eur J Immunol* 1994;24:3194–198.
47. Alt JA, Sautter NB, Mace JC, Detwiller KY, Smith TL. Antisomnogenic cytokines, quality of life, and chronic rhinosinusitis: a pilot study. *Laryngoscope* 2014;124:E107–E114.
48. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry* 2010;67:446–457.
49. Tsuno N, Besset A, Ritchie K. Sleep and depression. *J Clin Psychiatry* 2005;66:1254–1269.
50. Schlosser RJ, Storck K, Cortese BM, Uhde TW, Rudmik L, Soler ZM. Depression in chronic rhinosinusitis: A controlled cohort study. *Am J Rhinol Allergy* 2016;30:128–133.
51. Wong ML, Inserra A, Lewis MD, et al. Inflammasome signaling affects anxiety- and depressive-like behavior and gut microbiome composition. *Mol Psychiatry* 2016;21:797–805.
52. Burke NN, Finn DP, Roche M. Neuroinflammatory mechanisms linking pain and depression. *Mod Trends Pharmacopsychiatri* 2015;30:36–50.
53. Ghaffar O, Lavigne F, Kamil A, Renzi P, Hamid Q. Interleukin-6 expression in chronic sinusitis: colocalization of gene transcripts to eosinophils, macrophages, T lymphocytes, and mast cells. *Otolaryngol Head Neck Surg* 1998;118:504–511.
54. Lennard CM, Mann EA, Sun LL, Chang AS, Bolger WE. Interleukin-1 beta, interleukin-5, interleukin-6, interleukin-8, and tumor necrosis factor-alpha in chronic sinusitis: response to systemic corticosteroids. *Am J Rhinol* 2000;14:367–373.
55. Cox DR, Ashby S, DeConde AS, et al. Dyad of pain and depression in chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2016;6:308–314.
56. Illi J, Miaskowski C, Cooper B, et al. Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression. *Cytokine* 2012;58:437–447.
57. Thomas AJ, Orlandi RR, Ashby S, Mace JC, Smith TL, Alt JA. Nasal obstruction has a limited impact on sleep quality and quality of life in patients with chronic rhinosinusitis. *Laryngoscope* 2016;126:1971–1976.
58. Mullol J, Xaubet A, Lopez E, Roca-Ferrer J, Picado C. Comparative study of the effects of different glucocorticosteroids on eosinophil survival primed by cultured epithelial cell supernatants obtained from nasal mucosa and nasal polyps. *Thorax* 1995;50:270–274.
59. Schmidt EM, Linz B, Diekelmann S, Besedovsky L, Lange T, Born J. Effects of an interleukin-1 receptor antagonist on human sleep, sleep-associated memory consolidation, and blood monocytes. *Brain Behav Immun* 2015;47:178–185.
60. Opp MR, Postlethwaite AE, Seyer JM, Krueger JM. Interleukin 1 receptor antagonist blocks somnogenic and pyrogenic responses to an interleukin 1 fragment. *Proc Natl Acad Sci U S A* 1992;89:3726–3730.
61. Kubota T, Brown RA, Fang J, Krueger JM. Interleukin-15 and interleukin-2 enhance non-REM sleep in rabbits. *Am J Physiol Regul Integr Comp Physiol* 2001;281:R1004–R1012.
62. Seleznev KH, Barynov EF, Iel'skiy KV, Ziablitshev SV. [Interleukin-2 and interleukin-4 blood levels in sinusitis]. *Fiziol Zh* 2001;47:69–73.
63. Kushikata T, Fang J, Wang Y, Krueger JM. Interleukin-4 inhibits spontaneous sleep in rabbits. *Am J Physiol* 1998;275:R1185–R1191.
64. Garcia-Garcia F, Yoshida H, Krueger JM. Interleukin-8 promotes non-rapid eye movement sleep in rabbits and rats. *J Sleep Res* 2004;13:55–61.
65. Bauer J, Hohagen F, Ebert T, et al. Interleukin-6 serum levels in healthy persons correspond to the sleep-wake cycle. *Clin Invest* 1994;72:315.
66. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab* 1999;84:2603–2607.
67. Hogan D, Morrow JD, Smith EM, Opp MR. Interleukin-6 alters sleep of rats. *J Neuroimmunol* 2003;137:59–66.
68. Rothaug M, Becker-Pauly C, Kruse-John S. The role of interleukin-6 signaling in nervous tissue. *Biochim Biophys Acta* 2016;1863:1218–1227.
69. Oyanedel CN, Kelemen E, Scheller J, Born J, Rose-John S. Peripheral and central blockade of interleukin-6 trans-signaling differentially affects sleep architecture. *Brain Behav Immun* 2015;50:178–185.
70. Kushikata T, Fang J, Krueger JM. Interleukin-10 inhibits spontaneous sleep in rabbits. *J Interferon Cytokine Res* 1999;19:1025–1030.
71. Toth LA, Opp MR. Cytokine- and microbially induced sleep responses of interleukin-10 deficient mice. *Am J Physiol Regul Integr Comp Physiol* 2001;280:R1806–R1814.
72. Jyonouchi H, Sun S, Le H, Rimell FL. Evidence of dysregulated cytokine production by sinus lavage and peripheral blood mononuclear cells in patients with treatment-resistant chronic rhinosinusitis. *Arch Otolaryngol Head Neck Surg* 2001;127:1488–1494.
73. Kubota T, Fang J, Kushikata T, Krueger JM. Interleukin-13 and transforming growth factor-beta1 inhibit spontaneous sleep in rabbits. *Am J Physiol Regul Integr Comp Physiol* 2000;279:R786–R792.
74. al Ghamdi K, Ghaffar O, Small P, Frenkiel S, Hamid Q. IL-4 and IL-13 expression in chronic sinusitis: relationship with cellular infiltrate and effect of topical corticosteroid treatment. *J Otolaryngol* 1997;26:160–166.
75. Reh DD, Ramanathan M Jr, Sultan B, Wang Y, May L, Lane AP. The role of hepatocyte growth factor/c-Met in chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy* 2010;24:266–270.
76. Xu R, Xu G, Shi J, Wen W. A correlative study of NF-kappaB activity and cytokines expression in human chronic nasal sinusitis. *J Laryngol Otol* 2007;121:644–649.
77. Lane AP, Truong-Tran QA, Myers A, Bickel C, Schleimer RP. Serum amyloid A, properdin, complement 3, and toll-like receptors are expressed locally in human sinonasal tissue. *Am J Rhinol* 2006;20:117–123.
78. Okano M, Fujiwara T, Makihara S, et al. Characterization of IL-18 expression and release in the pathogenesis of chronic rhinosinusitis. *Int Arch Allergy Immunol* 2013;160:275–286.
79. Bohnet SG, Traynor TR, Majde JA, Kacsob B, Krueger JM. Mice deficient in the interferon type I receptor have reduced REM sleep and altered hypothalamic hypocretin, prolactin and 2',5'-oligoadenylate synthetase expression. *Brain Res* 2004;1027:117–125.
80. Kubota T, Li N, Guan Z, Brown RA, Krueger JM. Intrapreoptic microinjection of TNF-alpha enhances non-REM sleep in rats. *Brain Res* 2002;932:37–44.
81. Shin SH, Ponikau JU, Sherris DA, et al. Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. *J Allergy Clin Immunol* 2004;114:1369–1375.
82. Kou W, Hu GH, Yao HB, et al. Regulation of transforming growth factor-beta1 activation and expression in the tissue remodeling involved in chronic rhinosinusitis. *ORL J Otorhinolaryngol Relat Spec* 2012;74:172–178.
83. Tashiro M, Mochizuki H, Iwabuchi K, et al. Roles of histamine in regulation of arousal and cognition: functional neuroimaging of histamine H1 receptors in human brain. *Life Sci* 2002;72:409–414.
84. Ikeda-Sagara M, Ozaki T, Shahid M, et al. Induction of prolonged, continuous slow-wave sleep by blocking cerebral H(1) histamine receptors in rats. *Br J Pharmacol* 2012;165:167–182.
85. Okuda M, Watase T, Mezawa A, Liu CM. The role of leukotriene D4 in allergic rhinitis. *Ann Allergy* 1988;60:537–540.
86. Sri Kantha S, Matsumura H, Kubo E, et al. Effects of prostaglandin D2, lipoxins and leukotrienes on sleep and brain temperature of rats. *Prostaglandins Leukot Essent Fatty Acids* 1994;51:87–93.
87. Perez-Novo CA, Claeys C, Van Cauwenberge P, Bachert C. Expression of eicosanoid receptors subtypes and eosinophilic inflammation: implication on chronic rhinosinusitis. *Respir Res* 2006;7:75.
88. Sartorius T, Lutz SZ, Hoene M, et al. Toll-like receptors 2 and 4 impair insulin-mediated brain activity by interleukin-6 and osteopontin and alter sleep architecture. *FASEB J* 2012;26:1799–1809.
89. Lauriello M, Micera A, Muzi P, Di Rienzo Businco L, Bonini S. TLR4 and TLR9 expression in different phenotypes of rhinitis. *Int J Otolaryngol* 2012;2012:925164.