

# Sleep Dysfunction and its Association to Chronic Rhinosinusitis: 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 the billions of dollars annually in the United States. Chronic rhinosinusitis (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 rhinosinusitis, sleep dysfunction.

**Level of Evidence:** N/A.

## INTRODUCTION

Sleep is vital for overall health, wellness, and emotional well-being.<sup>1</sup> Deficient sleep negatively effects daily performance, quality of life (QOL), and mood.<sup>1</sup> 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.<sup>2-4</sup>

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

poor sleep quality (SQ) at significantly higher rates than the general population.<sup>5-12</sup> Chronic rhinosinusitis 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.<sup>13</sup> 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.<sup>14-18</sup> 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.<sup>19,20</sup>

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,

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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 <sup>57</sup>	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 <sup>17</sup>	2016	Prospective observational cohort	Refractory CRS undergoing ESS	SNOT-22	Following ESS, patients report significant and sustained improvements in sleep-related symptoms
Alt <sup>16</sup>	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 <sup>15</sup>	2015	Prospective observational cohort	CRSsNP undergoing ESS w/o septoplasty	EpSS, PSQI, SNOT-22, NOSE	Sleep outcomes improved following ESS
Alt <sup>14</sup>	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 <sup>5</sup>	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 <sup>37</sup>	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 <sup>36</sup>	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 <sup>17</sup>	2016	Prospective observational cohort	Refractory CRS undergoing ESS	SNOT-22	Following ESS, patients report significant and sustained improvements in sleep-related symptoms
Alt <sup>16</sup>	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 <sup>15</sup>	2015	Prospective observational cohort	CRSsNP undergoing ESS w/o septoplasty	EpSS, PSQI, SNOT-22, NOSE	ESS improved sleep outcomes
Alt <sup>14</sup>	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 <sup>37</sup>	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 <sup>36</sup>	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 polyps; 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 $\beta$	$\uparrow \leftrightarrow \downarrow$	$\uparrow$	+	Krueger <sup>41</sup> , Lennard <sup>54</sup> , Mullo <sup>58</sup> , Schmidt <sup>59</sup>
IL-1 R1	$\downarrow$			Opp <sup>42,43,60</sup> , Schmidt <sup>59</sup>
IL-2	$\uparrow$			Kubota <sup>61</sup> , Seleznev <sup>62</sup>
IL-4	$\downarrow$		+	Krueger <sup>41</sup> , Kushikata <sup>63</sup> , Lennard <sup>54</sup>
IL-8	$\uparrow$		+	Seleznev <sup>62</sup> , Garcia-Garcia <sup>64</sup> , Mullo <sup>58</sup>
IL-6	$\downarrow$	$\downarrow$	+	Bauer <sup>65</sup> , Vgontzas <sup>66</sup> , Hogan <sup>67</sup> , Ghaffar <sup>53</sup> , Rothaug <sup>68</sup> , Oyanedel <sup>69</sup>
IL-10	$\downarrow$		+	Krueger <sup>41</sup> , Kushikata <sup>70</sup> , Opp <sup>43</sup> , Toth <sup>71</sup> , Jyonouchi <sup>72</sup>
IL-13	$\downarrow$		+	Kubota <sup>73</sup> , al Ghamdi <sup>74</sup> , Reh <sup>75</sup> , Lennard <sup>54</sup>
NF- $\kappa\beta$	$\uparrow$		+	Kubota <sup>73</sup> , Xu <sup>76</sup> , Lane <sup>77</sup>
IL-15	$\uparrow$			Kubota <sup>61</sup>
IL-18	$\uparrow$			Kubota <sup>61</sup> , Okano <sup>78</sup>
Interferon- $\alpha$	$\uparrow \leftrightarrow \downarrow$	$\downarrow$		Bohnet <sup>79</sup>
Interferon- $\gamma$	$\uparrow$			Kubota <sup>80</sup> , Shin <sup>81</sup>
TNF- $\alpha$	$\uparrow$		+	Krueger <sup>41</sup> , Kubota <sup>80</sup> , Lennard <sup>54</sup>
TGF- $\beta$	$\downarrow$			Kubota, Kuo <sup>82</sup>
Histamine	$\downarrow$			Tashiro <sup>83</sup> , Ikeda-Sagara <sup>84</sup>
CystLT	$\uparrow$			Okuda <sup>85</sup> , Sri-Kantha <sup>86</sup> , Perez-Novo <sup>87</sup>
Toll-Like Receptors 2	$\uparrow$		+	Sartorius <sup>88</sup> , Lane <sup>77</sup>
Toll-Like Receptors 4	$\uparrow$		+	Sartorius <sup>88</sup> , Lane <sup>77</sup> , Lauriello <sup>89</sup>

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

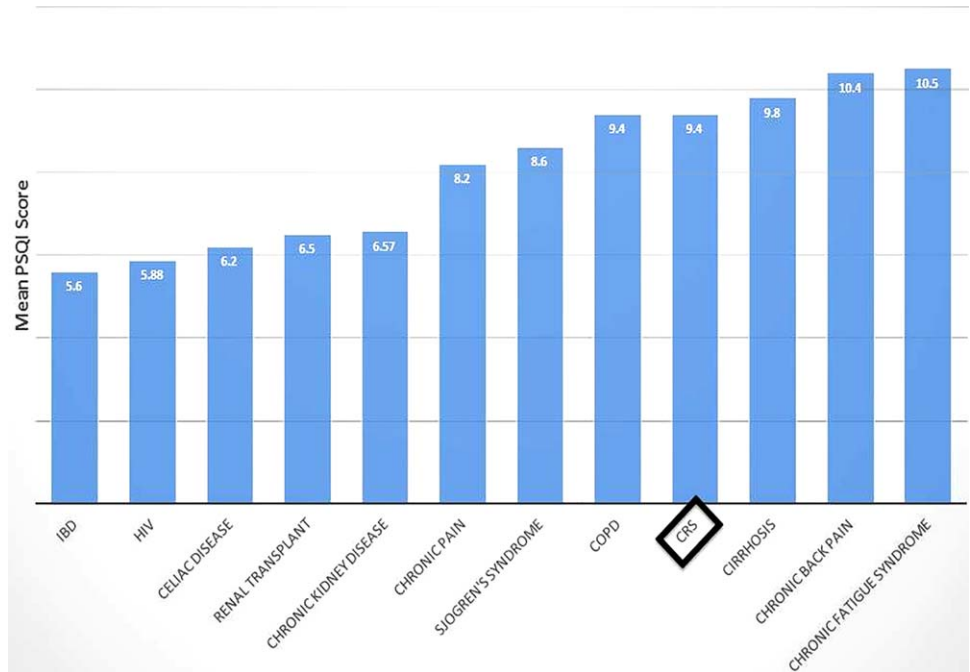


Fig. 1. Comparing mean PSQI scores for diseases associated with poor sleep quality

## 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).<sup>21</sup> 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.<sup>19,22</sup> 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.<sup>23</sup> 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.<sup>17</sup>

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.<sup>24-31</sup> In fact, only patients with chronic fatigue syndrome, chronic back pain, and cirrhosis reported worse SQ.<sup>32-35</sup> 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.<sup>14,28,31</sup> 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

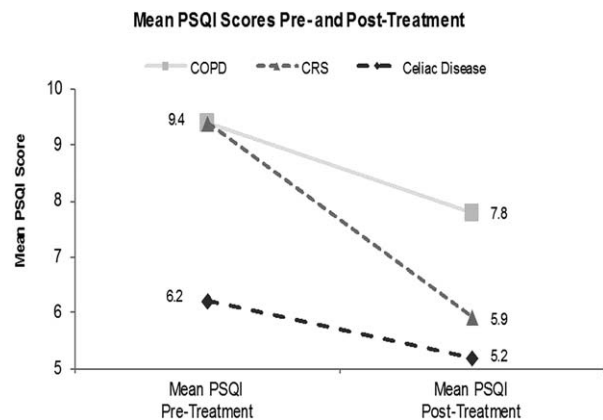


Fig. 2. Comparison of mean PSQI scores in patients before and after treatment of the underlying chronic disease

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.<sup>5</sup> 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.<sup>14</sup>

### **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.<sup>36</sup> 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.<sup>37</sup>

**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.<sup>38</sup> When patients do not respond to appropriate medical management, ESS is often considered as the next treatment option.<sup>38</sup> Multiple prospective studies evaluating sleep outcomes following ESS demonstrate significant improvements in subjective SQ scores on both the PSQI and EpSS (Table 4).<sup>14,15,17</sup> 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).<sup>14</sup> 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.<sup>39</sup>

**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 $\beta$  and tumor necrosis factor (TNF)- $\alpha$  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.<sup>40–44</sup> Conversely, cytokines that are upregulated in CRS such as IL-4, IL-13, and TGF- $\beta$  have been shown to antagonize the effects of IL-1 $\beta$  and TNF- $\alpha$  and act to decrease sleep.<sup>45,46</sup> 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- $\beta$  was associated with decreased SQ.<sup>47</sup> Additionally, IL-13 expression was associated with worse CRS specific disease severity scores and worse QOL.<sup>47</sup> 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.<sup>48</sup> 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.<sup>49</sup> Additionally, when compared to the general population, CRS patients have a higher prevalence of depression with nearly one-third of patients experiencing depressive symptoms.<sup>50</sup> Comorbid depression in patients with CRS has been shown to be an independent predictor of poor SQ.<sup>5</sup> 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.<sup>51,52</sup> Specifically, the cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 have all been found to be elevated in patients with chronic inflammatory diseases and comorbid depression.<sup>52</sup> These same cytokines are also elevated in patients with CRS (Table 4).<sup>53,54</sup> 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.<sup>52,55,56</sup> Furthermore, CRS patients with pain have been shown to have worse overall disease-specific QOL.<sup>55</sup> Similar to depression, chronic pain is independently associated with sleep dysfunction.<sup>30</sup> 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.

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