HHS Public Access

Author manuscript

Int Forum Allergy Rhinol. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Int Forum Allergy Rhinol. 2017 January ; 7(1): 56–63. doi:10.1002/alr.21843.

The Pain-Depression Dyad and the Association with Sleep Dysfunction in Chronic Rhinosinusitis

Daniel R. Cox, MD[1], **Shaelene Ashby, PhD**[1], **Jess C. Mace, MPH, CCRP**[2], **John M. DelGaudio, MD**[3], **Timothy L. Smith, MD MPH**[2], **Richard R. Orlandi, MD**[1], and **Jeremiah A. Alt, MD PhD**[1]

[1]Sinus and Skull Base Surgery Program, Division of Otolaryngology - Head and Neck Surgery, Department of Surgery; University of Utah, Salt Lake City, Utah, USA

[2]Rhinology and Skull Base Division, Department of Otolaryngology-Head and Neck Surgery, Oregon Health & Science University, Portland, OR, USA

[3]Rhinology and Anterior Skull Base, Department of Otolaryngology-Head and Neck Surgery, Emory University, Atlanta, GA, USA

Abstract

Background—Depression, pain, and sleep disturbance is a symptom cluster often found in patients suffering from chronic illness, exerting a large impact on quality-of-life (QOL). A wealth of literature exists demonstrating a significant association between depression, pain, and sleep dysfunction in other chronic diseases. This relationship has not been described in patients with chronic rhinosinusitis (CRS).

Methods—Sixty-eight adult patients with CRS were prospectively enrolled. Patients at risk for depression were identified using the Patient Health Questionnaire-2 (PHQ-2) using a cutoff of 1 or greater. Pain experience was measured using the Brief Pain Inventory Short Form (BPI-SF) and the Short Form McGill Pain Questionnaire (SF-MPQ). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI).

Results—Forty-seven patients were at risk for depression. Significant positive correlations were found between total PSQI scores and all pain measures ($R=0.38–0.61$, $p\leq0.05$) and between total PSQI scores and PHQ-2 scores ($R=0.46$, $p<0.05$). For patients at risk for depression, significant, positive correlations were found between pain measures, the total PSQI score, and the three PSQI subdomains (sleep latency, sleep quality, and daytime dysfunction; $R=0.31$-0.61, $p<0.05$). The relationship between pain and sleep dysfunction scores was not seen in the absence of depression.

Corresponding Author: Jeremiah A. Alt, MD, PhD, University of Utah, Department of Surgery; Division of Otolaryngology – Head & Neck Surgery, Sinus and Skull Base Surgery Program, 50 North Medical Drive, SOM 3C120, Salt Lake City, Utah 84132, PH: 801-587-8368, FAX: 801-585-5744, jeremiah.alt@hsc.utah.edu.

Conflict of Interest: None

Financial Disclosures: There are no relevant financial disclosures for Daniel R. Cox, Shaelene Ashby, or John M. DelGaudio for this investigation.

Accepted for oral presentation to the American Rhinologic Society during the 119th annual Combined Otolaryngologic Spring Meeting (COSM) in Chicago, IL, May 18-22nd, 2016.

Conclusions—Depression, pain, and sleep dysfunction are inter-related in patients with CRS. In the absence of depression significant correlations between pain and sleep are not observed, suggesting that depression plays a key role in this interaction. Further research investigating the complex relationship between depression, pain, and sleep dysfunction in CRS is needed.

Keywords

Outcome assessment; chronic disease; depression; sleep; pain; sinusitis

INTRODUCTION

The combination of pain, sleep dysfunction, and depression is a symptom cluster often found in patients suffering from chronic illness, exerting a substantial impact on quality-of-life (QOL) in this population. Recent studies have demonstrated significant correlations between pain, sleep dysfunction, and depression in a variety of chronic illnesses including diabetic peripheral neuropathy[1], chronic pain syndromes[2-4], cancer[5,6] and rheumatoid arthritis[7,8] among others.[9]

While the relationship between pain, sleep dysfunction, and depression has been studied in patients suffering from other chronic illnesses, no studies to date have attempted to describe the complex interplay between these symptoms in patients with chronic rhinosinusitis (CRS). Individual assessments of these symptoms in patients with CRS have, however, shown an increased burden of disease compared to controls.[10] For example, using validated instruments to assess pain, DeConde et al. showed that patients with CRS have more facial pain compared to controls, and pain correlated with CRS disease-specific QOL measures.[11] In a recent study by Alt et al., 75% of patients with CRS reported poor sleep scores using the Pittsburgh Sleep Quality Index (PSQI) [12] while Schlosser et al. recently demonstrated higher rates of depression in patients with CRS compared to controls based on Beck Depression Inventory scores.[13]

Our group recently showed that facial pain scores using validated pain questionnaires correlated significantly with the sleep dysfunction domain scores of the 22-item SinoNasal Outcome Test (SNOT-22) in patients who have depressive symptoms, but did not correlate significantly in patients without depressive symptoms, suggesting a potential link between pain, depression and sleep dysfunction in patients with CRS.[14] For this investigation we hypothesized that facial pain, sleep dysfunction, and depressive symptoms were associated in patients with CRS. Our objective was to further investigate evidence for these complex associations using validated instruments for assessing pain, depressive symptoms and sleep quality.

MATERIALS & METHODS

Subjects and Data Collection

Study participants were enrolled from the University of Utah Sinus and Skull base clinic. Patients meeting inclusion criteria were adult patients with the diagnosis of CRS according to the 2015 American Academy of Otolaryngology Adult Sinusitis Guideline.[15]

Study participants completed necessary enrollment procedures and provided informed consent. Study-related questionnaires completed by participants include the PSQI, the Patient Health Questionnaire-2 (PHQ-2), the Brief Pain Inventory Short Form (BPI-SF), and the Short-Form McGill Pain Questionnaire (SF-MPQ).

Demographic information and medical/social history were obtained from each study participant, including: age, gender, asthma, acetylsalicylic acid (ASA) sensitivity, allergy, current tobacco use, alcohol consumption, prior sinus surgery and previous diagnosis of obstructive sleep apnea (OSA). Approval from the University of Utah Institutional Review Board (IRB #61810) was obtained.

Exclusion criteria

Patients with an autoimmune and/or inflammatory disease such as rheumatoid arthritis or systemic lupus erythematosus (SLE) or with underlying severe or debilitating illnesses such as multiple sclerosis, cancer, cystic fibrosis (CF), or heart failure were excluded given the high likelihood of comorbid depressive symptoms, pain, and sleep dysfunction in this population. Patients with chronic pain conditions including fibromyalgia and chronic migraines, as well as those with a history of obstructive sleep apnea (OSA), were excluded from the analysis. In addition, all study participants who failed to complete all study-related questionnaires during the initial enrollment meeting were excluded.

Research Instruments

Pittsburgh Sleep Quality Index—The PSQI is a validated instrument to evaluate sleep quality.[16] It asks participants to answer questions pertaining to sleep quality during the past month. There is a total score (range: 0-21) and 7 subdomain scores (range: 0-3 for each) including those for: sleep quality, latency, duration, efficiency, disturbance, sleep medication use, and daytime dysfunction. Higher PSQI scores indicate poorer sleep quality. A PSQI total score < 5 is considered the threshold for “good” sleep quality while a total score > 5 represents “poor” sleep quality.

Patient Health Questionnaire-2—The PHQ-2 is comprised of the first two questions of the Patient Health Questionnaire-9 (PHQ-9). It has been validated as a screening tool to identify patients who are at-risk for depression.[17] Participants report how frequently they have experienced 1) little interest or pleasure in doing things and 2) feeling down, depressed, or hopeless in the past two weeks on a scale from 0 (not at all) to 3 (nearly every day). Patients were divided into two groups based on PHQ-2 score. Patients with a PHQ-2 score of ≥ 1 were designated as being at risk for any depressive disorder (n=47), and those with a PHQ-2 score of 0 were designated as not at risk for any depressive disorder (n=23). The commonly accepted cutoff for the PHQ-2 is ≥ 3, however it has been suggested that if the instrument is being used as a screening tool for depressive disorder, a cutoff of ≥ 3 may result in an unacceptably high false negative rate[18]. We therefore opted to use a score of ≥ 1 to define patients at risk for depression.

Brief Pain Inventory Short Form—The BPI-SF measures pain intensity and the extent to which pain interferes with daily activities. It has been validated for use in chronic pain

and has recently been used to examine facial pain in patients with CRS.[11] For the present study, the questionnaire was modified to specifically assess facial pain. Participants rate their current pain level on a 0-10 scale with larger numbers representing more severe pain. Participants also rate their pain at its "worst," "least," and "average" on a 0-10 scale. The final pain severity score is the mean of the four values (range 0-10). Pain interference is assessed by asking participants to rate the level of interference their pain causes in 7 different categories including: general activity, walking ability, work, mood, enjoyment of life, relations with other people, and sleep. These are also rated on a 0-10 scale with higher scores representing more interference. The pain interference score is calculated as the mean of the interference items (range: 0-10).

Short Forum McGill Pain Questionnaire—The SF-MPQ consists of 15 items relating to pain quality.[19] As with the BPI-SF, this questionnaire was also modified to address facial pain specifically. Patients rate their pain experience with regard to each item on a scale of 0 (none) to 3 (severe). The first 11 items represent the sensory dimension of pain, while the remaining 4 represent the affective dimension. Totals in each dimension are calculated (ranges: sensory 0-33, affective 0-12, total 0-45). In addition, participants rate their current pain (Present Pain Inventory, PPI) on a 0-5 scale with higher scores representing more severe pain. The final total score of the SF-MPQ is calculated as the sum of the PPI and the total score of the sensory and affective dimensions (range 0-50). Finally, the SF-MPQ includes a visual analogue scale (VAS) to indicate overall pain intensity. For the current study, the VAS was modified to a Likert scale from 0-10 and participants were asked to refer only to sinus pain.

Data Management, Sampling Size Estimations, and Statistical Analysis

Study data were collected using standardized research instruments. All participants were assigned a unique study identifier to ensure confidentiality. Data were manually entered into an electronic database (Microsoft Access; Microsoft Corp., Redmond, WA) by a trained research coordinator. SPSS (IBM Corp., Armonk, NY, Version 22.0) statistical software was used for data analysis. An estimated sample size was calculated for bivariate correlation coefficients (R) between pain and depression. Calculations assumed 80% power (1-β error probability) and a 0.050 alpha (α) level. Results of the power analysis suggest that the current sample size has the power to detect a significant correlation coefficient of $R \geq 0.324$.

Descriptive statistics were calculated to summarize patient characteristics, such as age, gender, and other health conditions. Bivariate Spearman (R_s) correlations were used to identify associations between pain, depression, and sleep scores among patients with CRS.

RESULTS

A total of 68 patients qualified for the study based on inclusion and exclusion criteria and were prospectively enrolled between August, 2013-October, 2015. Study group demographic characteristics are summarized in **Table 1**. Demographic and clinical characteristics for patients at risk versus not at risk for depression are compared in **Table 2**. Patients at risk for depression had significantly higher prevalence of prior surgery compared to those not at risk

for depression. Otherwise, there were no statistically significant differences observed between the two groups across patient characteristics.

Bivariate correlation analysis was performed for PSQI scores and pain severity measures. Significant positive correlations were found between overall PSQI scores and all pain measures **(Table 3)**. PSQI subdomain analysis also revealed positive correlations between facial pain measures and PSQI subdomain scores (**Table 3**). The R-values reported here are in the range of what is conventionally considered to be 'mild' to' moderate' in magnitude[20]. The strongest correlations were seen between SF-MPQ scores and the sleep latency, daytime dysfunction, sleep quality, and medication use subdomains.

Association between depression and sleep measures are described in **Tables 4-5**. Significant positive associations were identified between PHQ-2 and PSQI total scores. When the PSQI was divided into subdomains, significant positive correlations were seen between PHQ-2 scores and all PSQI subdomain scores except sleep efficiency. Again, these correlations were in the mild to moderate range. Additionally, patients at risk for depression had significantly higher mean PSQI total scores than those not at risk for depression. When the patients were stratified into "good" vs "poor" sleep quality subgroups, patients with "poor" sleep quality who were at risk for depression had significantly higher PSQI scores than those not at risk for depression. This relationship was not seen in patients with "good" sleep quality.

Finally, we sought to delineate the relationship between pain, sleep and depression scores in CRS (**Table 6**). There were significant positive correlations between facial pain measures and all PSQI subdomains in patients at risk for depression. The correlations were again mild to moderate in strength, with the strongest correlations seen in the sleep latency, daytime dysfunction, sleep quality, and medication use subdomain scores. For patients not at risk for depression, associations between PHQ-2 scores and PSQI scores were substantially less frequent and were seen only in the sleep disturbance and medication use subdomains.

DISCUSSION

Individuals with chronic illnesses often experience a number of comorbid ailments that disturb overall QOL. Pain, depression, and sleep dysfunction are among these, and this symptom constellation is often seen in patients with CRS. The relationship between these three symptom constructs has been investigated in other chronic illnesses, but has not been well delineated in CRS. In the present study, we demonstrated correlations between reported pain, sleep and depression scores in patients with CRS. We found significant correlations between sleep quality scores and pain measures. We also demonstrated significant correlations between sleep quality scores and PHQ-2 scores. Patients at risk for depression had significantly higher scores on the PSQI than those not at risk for depression. Additionally, we demonstrated that pain measures and PSQI scores were correlated to a large degree in patients at risk for depression, but this association was markedly diminished in those not at risk for depression. Taken together, these findings suggest some magnitude of association between facial pain, depressive symptoms, and sleep dysfunction in CRS.

The associations between facial pain, sleep dysfunction and depression in patients with CRS that were found in the present study raise some interesting questions about whether there is a plausible pathobiologic mechanism that could explain these associations. Although this has not been studied in CRS, several possibilities have been posited in other fields. For example, it is known that pain, sleep, and mood share common neurobiological pathways, and it has been suggested that alterations in these pathways could be responsible for the association. For example, disturbance in the mesolimbic dopamine signaling system has been extended as a putative mechanism.[21] Mesolimbic dopaminergic neurons originate in the ventral tegmental area and project to a number of locations in the brain known to be related to sleep and wakefulness.[22] In vivo models have suggested that increased dopamine levels in these areas is related to the arousal-promoting effects of exogenous stimulants and the resultant sleep disturbance/insomnia.[23-25] In addition, phasic release of dopamine in the mesolimbic system produces analgesia in response to a pain stimulus. Studies have shown that increased tonic dopamine levels in the mesolimbic system results in decreased sensitivity to phasic dopamine release leading to increased pain response to an acute pain stimulus.[26] This decreased phasic dopamine release is also believed to be related to the development of depression and anhedonia.[27,28] This body of evidence suggests that persistent elevation of tonic dopamine levels in the mesolimbic system is at least a plausible explanation for the correlation and interaction between sleep dysfunction, pain and depression in patients suffering from chronic illness.

Other neurobiological signaling pathways are also known to play a role in depression, sleep regulation, and pain modulation, and may be implicated in this triad. Serotonin, for example, has long been recognized as a key regulatory neurotransmitter in the sleep/wake cycle.[29] Serotonin is also believed to play a crucial role in the pathobiology of depression[30], and has been implicated in pain modulation.[31] Some authors have therefore suggested serotonergic signaling dysfunction as the underlying mechanism linking pain, sleep dysfunction, and depression in patients with chronic illness.[32] Other neurotransmitters including norepinephrine have also been suggested to contribute.

Perhaps more intriguing is the idea that inflammation may contribute to this symptom constellation through what has been referred to as the “immune brain pathway.” There are a number of studies describing the role of pro-inflammatory cytokines in sleep regulation, specifically IL-1 and TNF.[33] The effects of inflammatory cytokines on pain and depression have also been described. A recent systematic review by Howren et al. found positive associations between depression and IL-1, CRP, and IL-6.[34] TNF and IL-1 have also been shown to modulate pain perception.[35,36] Doong et al. demonstrated that variations in pro- and anti-inflammatory genes are associated with pain, fatigue, sleep disturbance, and depression in patients with breast cancer.[5] These inflammatory cytokines are known to be up regulated in CRS.[33] These findings support the notion that sinonasal inflammation may play a role in the complex interaction between pain, sleep dysfunction, and depression in CRS.

In the current study, we demonstrated correlations between facial pain measures and PSQI scores in patients at risk for depression based on PHQ-2 screening scores. For patients not at risk for depression, these associations were markedly decreased. This supports the findings of our prior study in which we demonstrated significant positive correlations between all

pain measures and the sleep dysfunction domain of the SNOT-22 in patients at risk for depression, but not in patients not at risk for depression.[14] The loss of association between pain and sleep dysfunction in the absence of depression suggests that depression may play a key role in the interplay between these symptoms.

We have shown that patients with CRS who are at risk for depression experience significantly more facial pain and sleep dysfunction than those not at risk for depression.[14] It is not currently known whether patients have more facial pain and sleep dysfunction because they are depressed or if they experience more depressive symptoms because of facial pain or sleep dysfunction. The relationship between these symptoms is likely highly complex and studies aimed at determining which, if any, of these symptoms is the driving force behind this interaction are warranted.

Research efforts focused on better understanding this complex relationship in CRS may help inform treatment strategies and improve outcomes. Recent research has shown that depression predicts worse QOL outcomes after endoscopic sinus surgery.[37,38] In light of the results of the current study, the question arises of whether managing comorbid depressive symptoms would improve outcomes in CRS. The effect of antidepressant therapy in patients with CRS has not been investigated to date. Additional investigations are needed to determine if there is a benefit to managing depression in CRS.

Interestingly, we found that patients in our cohort who were at risk for depression had significantly higher prevalence of prior sinus surgery compared to those not at risk for depression. A recent study by Orb et al[39] showed that after an initial period of medical management, patients with CRS electing endoscopic sinus surgery over continued medical management had significantly higher scores on the emotional subdomains of the RSDI compared with those who opted for continued medical management, suggesting that, in some patients, emotional forces may be influencing the decision to pursue surgery. This could explain the higher incidence of prior sinus surgery in those at risk for depression in our cohort. Alternatively, it may be that prior sinus surgery had an effect on the emotional state of patients thereby increasing depressive symptoms. Further research is needed to better clarify this relationship.

We used the PHQ-2 to detect depressive symptoms in our patient population. Historically, a score of 3 or greater has been used to define patients who are at risk for depression due to an instrument sensitivity of 83% and a specificity of 92% for major depression[17]. More recently, it has been suggested that a cutoff of ≥ 3 has an unacceptably high false negative rate for a screening instrument.[18] Using a cutoff score of 1 or greater, the PHQ-2 has a sensitivity and specificity of 97.6% and 59.2%, respectively, for detection of major depressive disorder, and a sensitivity and specificity of 90.6% and 65.4%, respectively, for detection of any depressive disorder. We elected to use a score threshold of 1 or greater, instead of the traditional cutoff of ≥ 3 in order to decrease the risk of misclassifying at-risk patients.

It is important to point out that although statistically significant and the R-values observed are in the range of what is generally accepted as mild to moderate in strength. Additionally,

there is currently no defined minimum clinically important difference (MCID) for the PSQI. Therefore, it is unknown whether the difference in PSQI scores between patients at-risk and not at-risk for depression (**Table 5**) is clinically significant. Further defining the clinical relevance of these findings is an area of potential future study.

Strengths of the current study include a prospective design and utilization of validated instruments to assess pain, depression, and sleep dysfunction. One limitation is that patients were enrolled exclusively through a tertiary sinus clinic located in an academic center. Patients enrolled in this setting may not be comparable to those seen in the community setting, and the results may therefore not be externally generalizable. Additionally, we did not attempt to control for, or exclude patients based on, current medication use. There are a number of medications including anti-depressants and anxiolytics which act on the central nervous system and could have affected the relationships seen between pain, sleep dysfunction, and depressive symptom scores.

CONCLUSION

Depression, pain, and sleep dysfunction are interrelated in patients with CRS. The relationship between pain and sleep dysfunction is lost in the absence of depression, suggesting that depression may play a key role in this interaction. Further research investigating the complex relationship between depression, facial pain, and sleep dysfunction in CRS is needed.

Acknowledgments

Jeremiah A. Alt, Jess C. Mace, and Timothy L. Smith were supported for this investigation by a grant from the National Institute on Deafness and Other Communication Disorders (NIDCD), one of the National Institutes of Health, Bethesda, MD (R01 DC005805; PI/PD: TL Smith). Public clinical trial registration number (www.clinicaltrials.gov) NCT01332136. Jeremiah A. Alt and Richard R. Orlandi are consultants for IntersectENT, Inc and Medtronic, Inc, which are not affiliated with this investigation.

REFERENCES

1. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. Journal of pain and symptom management. 2005; 30(4):374–385. [PubMed: 16256902]
2. Annagur BB, Uguz F, Apiliogullari S, Kara I, Gunduz S. Psychiatric disorders and association with quality of sleep and quality of life in patients with chronic pain: a SCID-based study. Pain Med. 2014; 15(5):772–781. [PubMed: 24612225]
3. Campbell P, Tang N, McBeth J, et al. The role of sleep problems in the development of depression in those with persistent pain: a prospective cohort study. Sleep. 2013; 36(11):1693–1698. [PubMed: 24179303]
4. Emery PC, Wilson KG, Kowal J. Major depressive disorder and sleep disturbance in patients with chronic pain. Pain Res Manag. 2014; 19(1):35–41. [PubMed: 24367795]
5. Doong SH, Dhruva A, Dunn LB, et al. Associations between cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression in patients prior to breast cancer surgery. Biol Res Nurs. 2015; 17(3):237–247. [PubMed: 25304131]
6. Ho SY, Rohan KJ, Parent J, Tager FA, McKinley PS. A longitudinal study of depression, fatigue, and sleep disturbances as a symptom cluster in women with breast cancer. Journal of pain and symptom management. 2015; 49(4):707–715. [PubMed: 25461671]

7. Irwin MR, Olmstead R, Carrillo C, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep. 2012; 35(4):537–543. [PubMed: 22467992]
8. Nicassio PM, Ormseth SR, Kay M, et al. The contribution of pain and depression to self-reported sleep disturbance in patients with rheumatoid arthritis. Pain. 2012; 153(1):107–112. [PubMed: 22051047]
9. Parmelee PA, Tighe CA, Dautovich ND. Sleep disturbance in osteoarthritis: linkages with pain, disability, and depressive symptoms. Arthritis Care Res (Hoboken). 2015; 67(3):358–365. [PubMed: 25283955]
10. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. International forum of allergy & rhinology. 2016; 6(Suppl 1):S22–S209. [PubMed: 26889651]
11. DeConde AS, Mace JC, Ashby S, Smith TL, Orlandi RR, Alt JA. Characterization of facial pain associated with chronic rhinosinusitis using validated pain evaluation instruments. International forum of allergy & rhinology. 2015; 5(8):682–690. [PubMed: 26074476]
12. Alt JA, Smith TL, Mace JC, Soler ZM. Sleep quality and disease severity in patients with chronic rhinosinusitis. The Laryngoscope. 2013; 123(10):2364–2370. [PubMed: 23918740]
13. Schlosser RJ, Storck K, Cortese BM, Uhde TW, Rudmik L, Soler ZM. Depression in chronic rhinosinusitis: A controlled cohort study. American journal of rhinology & allergy. 2016; 30(2): 128–133.
14. Cox DR, Ashby S, DeConde AS, et al. Dyad of pain and depression in chronic rhinosinusitis. International forum of allergy & rhinology. 2016; 6(3):308–314. [PubMed: 26954903]
15. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2015; 152(2 Suppl):S1–S39.
16. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28(2):193–213. [PubMed: 2748771]
17. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Medical care. 2003; 41(11):1284–1292. [PubMed: 14583691]
18. Arroll B, Goodyear-Smith F, Crengle S, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. Annals of family medicine. 2010; 8(4):348–353. [PubMed: 20644190]
19. Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987; 30(2):191–197. [PubMed: 3670870]
20. Cohen, J. Statistical power analysis for the behavioral sciences. 2nd ed.. Lawrence Erlbaum Associates; Hillsdale, NJ: 1988.
21. Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. Sleep Med Rev. 2013; 17(3):173–183. [PubMed: 22748562]
22. Lena I, Parrot S, Deschaux O, et al. Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep--wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. J Neurosci Res. 2005; 81(6):891–899. [PubMed: 16041801]
23. Qu WM, Huang ZL, Xu XH, Matsumoto N, Urade Y. Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil. J Neurosci. 2008; 28(34):8462–8469. [PubMed: 18716204]
24. Volkow ND, Fowler JS, Logan J, et al. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA. 2009; 301(11):1148–1154. [PubMed: 19293415]
25. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic role in stimulant-induced wakefulness. J Neurosci. 2001; 21(5):1787–1794. [PubMed: 11222668]
26. Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience. 1991; 41(1):1–24. [PubMed: 1676137]
27. Cabib S, Puglisi-Allegra S. Stress, depression and the mesolimbic dopamine system. Psychopharmacology (Berl). 1996; 128(4):331–342. [PubMed: 8986003]

28. Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006; 59(12):1151–1159. [PubMed: 16566899]
29. Ursin R. Serotonin and sleep. Sleep Med Rev. 2002; 6(1):55–69. [PubMed: 12531142]
30. Carver CS, Johnson SL, Joormann J. Serotonergic function, two-mode models of self-regulation, and vulnerability to depression: what depression has in common with impulsive aggression. Psychol Bull. 2008; 134(6):912–943. [PubMed: 18954161]
31. Kesic M, Tvrdeic A, Kolaric D, Stojkovic R, Cicin-Sain L. Serotonergic modulation of pain and analgesic responses: a study in rats with constitutionally altered serotonin transporters. Eur J Pain. 2015; 19(4):508–515. [PubMed: 25070859]
32. Ohayon MM. Pain sensitivity, depression, and sleep deprivation: links with serotoninergic dysfunction. J Psychiatr Res. 2009; 43(16):1243–1245. [PubMed: 19914447]
33. Alt JA, Smith TL. Chronic rhinosinusitis and sleep: a contemporary review. International forum of allergy & rhinology. 2013; 3(11):941–949. [PubMed: 24039230]
34. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosomatic medicine. 2009; 71(2):171–186. [PubMed: 19188531]
35. Andrade P, Hoogland G, Del Rosario JS, Steinbusch HW, Visser-Vandewalle V, Daemen MA. Tumor necrosis factor-alpha inhibitors alleviation of experimentally induced neuropathic pain is associated with modulation of TNF receptor expression. J Neurosci Res. 2014; 92(11):1490–1498. [PubMed: 24964368]
36. Oliveira A, Dinis-Oliveira RJ, Nogueira A, et al. Interleukin-1beta genotype and circulating levels in cancer patients: metastatic status and pain perception. Clin Biochem. 2014; 47(13-14):1209–1213. [PubMed: 24747159]
37. Brandsted R, Sindwani R. Impact of depression on disease-specific symptoms and quality of life in patients with chronic rhinosinusitis. American journal of rhinology. 2007; 21(1):50–54. [PubMed: 17283561]
38. Smith TL, Mendolia-Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattinger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. The Laryngoscope. 2005; 115(12):2199–2205. [PubMed: 16369166]
39. 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. International forum of allergy & rhinology. 2016; 6(3):315–321. [PubMed: 26536520]

Table 1

Baseline characteristics of study group (N=68)

Demographics/History	CRS	
	Mean [SD]	N [%]
Age (years)	49.12 [16.87]	
Males		36 [53]
Females		32 [47]
Asthma		35 [52]
ASA sensitivity		9 [13]
Allergy		35 [52]
Current tobacco use		4 [6]
Alcohol consumption		19 [28]
Prior sinus surgery		41 [60]
Pain Scores		
BPI-SF pain severity	3.39 [2.05]	
BPI-SF pain interference	3.40 [2.68]	
Total SF-MPQ	12.59 [10.29]	
Sensory dimension	9.70 [7.85]	
Affective dimension	3.00 [2.85]	
PPI	2.14 [1.31]	
Depression		
PHQ-2 score	1.81 [1.91]	
PHQ-2 Score ≥ 1		47 [69]
Sleep		
PSQI score (total)	9.85 [4.74]	
Disease Severity Measures:		
Lund-Mackay CT Score	12.71 [7.03]	
Lund-Kennedy Endoscopy Score	5.57 [3.41]	

SD = standard deviation; BPI-SF = Brief Pain Inventory Short Form; SF-MPQ = Short-Form McGill Pain Questionnaire; PPI = Present Pain Inventory; PHQ-2 = Patient Health Questionnaire–2; PSQI = Pittsburgh Sleep Quality Index.

Table 2

Comparison of baseline characteristics between patients with CRS at risk and not at risk for depression based on PHQ-2 scores.

Demographics/History	PHQ-2 ≥ 1		PHQ-2 = 0		p-value
	Mean [SD]	N [%]	Mean [SD]	N [%]	
Age (years)	47.34 [16.20]		53.10 [18.04]		0.196
Males		23 [48.9%]		13 [61.9%]	0.322
Asthma		21 [44.7%]		14 [66.7%]	0.094
ASA sensitivity		5 [10.6%]		4 [19.0%]	0.344
Allergy		23 [48.9%]		12 [57.1%]	0.333
Current tobacco use		4 [8.5%]		0 [0.0%]	0.168
Alcohol consumption		10 [21.3%]		9 [42.9%]	0.067
Prior sinus surgery		32 [68.1%]		9 [42.9%]	0.049*
SNOT-22 score	59.14 [18.67]		54.21 [19.58]		0.349
Lund-Mackay CT Score	11.91 [7.50]		14.50 [5.59]		0.173
Lund-Kennedy Endoscopy Score	5.36 [3.64]		6.05 [2.86]		0.465

SD = standard deviation; PHQ-2 = Patient Health Questionnaire–2

Table 3

Bivariate Spearman correlation coefficients between PSQI scores and pain severity measures for patients with CRS.

	PSQI Scores							
	Sleep Duration R_s	**Sleep Disturbance R_s**	**Sleep Latency R_s**	**Daytime Dysfunction R_s**	**Sleep Efficiency R_s**	**Sleep Quality R_s**	**Medication Use R_s**	**Total R_s**
BPI-SF Pain severity	0.191	0.131	0.229	0.394**	0.198	0.313*	0.380**	0.388**
BPI-SF Pain interference	0.397**	0.409**	0.444**	0.483**	0.172	0.459**	0.412**	0.587**
Total SF-MPQ	0.348**	0.407**	0.505**	0.449**	0.328*	0.575**	0.429**	0.613**
Sensory dimension	0.321*	0.392**	0.432**	0.420**	0.232	0.549**	0.441**	0.558**
Affective dimension	0.302*	0.373**	0.493**	0.421**	0.313*	0.514**	0.377**	0.585**
PPI Score	0.299*	0.154	0.427**	0.378**	0.235	0.392**	0.397**	0.455**
VAS Score	0.229	0.204	0.347**	0.370**	0.163	0.279*	0.416**	0.451**

R_S=correlation coefficient; BPI-SF = Brief Pain Inventory Short Form; SF-MPQ = Short-Form McGill Pain Questionnaire; PPI = Present Pain Inventory; VAS = Visual Analogue Scale; PSQI = Pittsburgh Sleep Quality Index.

*p<0.05

**p<0.01

Table 4

Bivariate Spearman correlation coefficient between PSQI score and PHQ-2 score for patients with CRS.

	PSQI Scores							
	Sleep Duration R_s	**Sleep Disturbance R_s**	**Sleep Latency R_s**	**Daytime Dysfunction R_s**	**Sleep Efficiency R_s**	**Sleep Quality R_s**	**Medication Use R_s**	**Total R_s**
PHQ-2 Score	0.314**	0.327**	0.298*	0.374**	0.220	0.335**	0.341**	0.457**

R_S=correlation coefficient; PSQI = Pittsburgh Sleep Quality Index; PHQ-2 = Patient Health Questionnaire–2

* p<0.05

** p<0.01

Table 5

Comparison of PSQI scores between patients with CRS at risk and not at risk for depression based on PHQ-2 scores.

	PHQ -2 1 or greater	PHQ-2 less than 1	
	Mean [SD]	Mean [SD]	p-value
PSQI Score	10.80 [4.76]	7.19 [3.54]	0.008*
Good Sleep Quality (PSQI ≤ 5)	4.33 [0.82]	3.67 [1.51]	0.369
Poor Sleep Quality (PSQI > 5)	11.79 [4.32]	9.30 [2.54]	0.027*

SD – standard deviation; PSQI = Pittsburgh Sleep Quality Index; PHQ-2 = Patient Health Questionnaire–2.

Table 6

Bivariate Spearman correlation coefficient between pain severity measures and PSQI scores in patients with CRS at risk and not at risk for depression based on PHQ-2 scores.

	Pain Severity Measures: PHQ-2 ≥ 1	PSQI Scores							
		Sleep Duration R_s	Sleep Disturbance R_s	Sleep Latency R_s	Daytime Dysfunction R_s	Sleep Efficiency R_s	Sleep Quality R_s	Medication Use R_s	Total R_s
At Risk for Depression	BPI-SF Pain severity	0.071	0.025	0.308*	0.393**	0.152	0.315*	0.280	0.305*
	BPI-SF Pain interference	0.319*	0.285	0.497**	0.491**	0.159	0.424**	0.447**	0.530**
	Total SF-MPQ	0.272	0.320*	0.528**	0.414**	0.365*	0.610**	0.376*	0.573**
	Sensory dimension	0.245	0.310*	0.500**	0.368*	0.262	0.590**	0.385**	0.536**
	Affective dimension	0.266	0.297	0.486**	0.345*	0.417**	0.537**	0.332*	0.543**
	PPI Score	0.230	0.050	0.446**	0.399**	0.143	0.398**	0.265	0.371*
	VAS Score	0.114	0.154	0.410**	0.316*	0.068	0.284	0.339*	0.331*

	Pain Severity Measures: PHQ-2 = 0	Sleep Duration R_s	Sleep Disturbance R_s	Sleep Latency R_s	Daytime Dysfunction R_s	Sleep Efficiency R_s	Sleep Quality R_s	Medication Use R_s	Total R_s
Not At Risk for Depression	BPI-SF Pain severity	0.248	0.144	−0.051	0.120	0.064	0.122	0.583*	0.218
	BPI-SF Pain interference	0.366	0.514*	0.175	0.113	0.012	0.418	0.317	0.417
	Total SF-MPQ	0.258	0.396	0.263	0.117	0.113	0.278	0.460	0.318
	Sensory dimension	0.161	0.231	0.111	0.203	0.057	0.213	0.513*	0.253
	Affective dimension	0.192	0.408	0.314	0.244	−0.112	0.275	0.372	0.275
	PPI Score	0.330	0.223	0.203	0.044	0.245	0.242	0.585*	0.385
	VAS Score	0.173	0.000	0.049	0.180	0.190	0.024	0.520*	0.370

R_S=correlation coefficient; BPI-SF = Brief Pain Inventory Short Form; SF-MPQ = Short-Form McGill Pain Questionnaire; PPI = Present Pain Inventory; VAS = Visual Analogue Scale; PSQI = Pittsburgh Sleep Quality Index; PHQ-2 = Patient Health Questionnaire–2.

*p-value<0.05

**p-value<0.01