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Sleep disturbances are associated with pain intensity and pain-related functional interference in patients experiencing orofacial pain

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Abstract

Background: Sleep and pain have a reciprocal relationship, interacting with psychosocial aspects including depression, anxiety, somatization and significant stressful events.

Objective: The aim of this study was to assess patients with oro-facial pain (OFP) and related sleep disturbances and determine the strongest psychosocial correlates.

Methods: A cross-sectional study of anonymized data of consecutive patients with OFP {January 2019 and February 2020} were analysed. Diagnostic and Axis-II data were integrated to assess the relationship between sleep disturbances, measured using Chronic Pain Sleep Inventory, and demographic factors, clinical comorbidities, recent stressful events, pain severity and pain- and psychological-related function.

Results: Five out of six patients with OFP were presented with pain-related sleep disturbances. Sleep problems were enhanced in patients with primary oro-facial headache compared with other OFP conditions. However, once the level of pain intensity and interference was accounted for, primary headache, was not a significant correlate of pain-related sleep disturbances. Multivariate analysis revealed (average) pain severity and pain interference were both significantly associated with sleep problems. There were also significant independent associations of sleep problems with somatization levels and reported experience of recent stressful events.

Conclusion: Identifying sleep problems as a part of OFP management may be beneficial and could result in better management outcomes.

KEYWORDS
oro-facial pain, pain intensity, pain interference, recent stressful event, sleep, somatization

1 | BACKGROUND

Numerous studies have shown that sleep problems/disturbances and chronic pain are highly comorbid. Earlier it was thought sleep and pain had a bidirectional relationship where a poor night sleep precipitates pain and pain in turn contributes to sleep disturbances.[1] However, recent longitudinal and micro-longitudinal studies point towards a more consistent unidirectional effect of

sleep predisposing individuals to the development of chronic pain or to the worsening of painful conditions.[2–4] Regardless of directionality, either co-existing or presented independently, sleep disturbances and chronic pain have a negative effect on physical, emotional and psychological health, thereby impacting individuals' quality of life.[4,5]

Few studies have focused on the potentially detrimental effects of sleep disturbance on pain intensity and function in patients with chronic pain after accounting for the mediating role of psychological distress. Findings from a heterogenous sample of chronic pain (more than 10% with head pain) patients[6] and chronic low back pain (CLBP)[7] showed sleep problems independently associate with chronic pain intensity even after controlling for depression and catastrophizing. Similarly, findings from a prior study, also with a heterogenous sample of chronic pain patients, reported sleep disturbances predicted disability independent of pain and depression.[8] This suggests that sleep disturbances may have their own independent contribution (to pain) over and above mutual association with psychological distress. Although such mediation analysis has not been performed in orofacial pain (OFP) populations, a study by Bhalang et al.[9] reported similar associations between sleep impairment and pain intensity and the author indicated that other psychological variables could have contributed to insomnia in addition to selected pain feature-pain intensity.

In the OFP population, one in three individuals reports sleep problems.[10] Female teenagers and older women with OFP tend to be more affected by sleep problems (insomnia/hypersomnia) than men with OFP. Changes in sleep often precede the new onset of future chronic Temporomandibular disorders (TMDs).[11] In a cohort of female TMD patients, depressive symptoms and low mood covary with pain ratings and provide a better explanation than pain for sleep problems.[12]

Besides a well-established relationship between sleep and pain, studies have demonstrated the interplay between sleep and psychological states of depression, anxiety and somatic complaints.[13,14] Mood alterations and increased bodily complaints are associated with sleep deprivation even in healthy adults.[15] OFP patients with headaches report higher pain intensity and somatic complaints.[16] Another component of interest is the role of stressful/adverse/traumatic events and the future development of sleep problems.[17,18] Individuals exposed to traumatic events report difficulty falling asleep[17] and increased awakening during the night.[17] Thus, sleep can interact with multiple factors such as demographics, clinical comorbidities, stressful events, affective functions and pain-related factors.

The aims of this study were to assess pain-specific sleep disturbances among a large cohort of patients with OFP with varying presentations, compare the magnitude of sleep problems according to OFP primary diagnosis and explore the associations between sleep problems and demographic factors, clinical comorbidities, recent stressful events, pain severity and pain- and psychological-related function.

2 | METHODS

Anonymized data were collected from consecutive patients seen at a multidisciplinary orofacial pain clinic at King's college hospital between January 2019 and February 2020. Demographic data, diagnosis and OFP duration were collected from clinic letters and case notes. A diagnosis or diagnoses of more than one condition were made by a team of Oral surgeon/OFP Pain specialist and Neurologist and a liaison Psychiatrist. All diagnoses were conformed to align with the International Classification of Orofacial Pain (ICOP),[19] whereas all TMD diagnoses were made using Diagnostic Criteria for Temporomandibular Disorders.[20] Diagnosis of primary headaches and their subtype were expanded to include all three types of patients who seem to represent crossroads of headache and OFP and hence categorized as 'Primary headaches presenting in orofacial region' vs 'Orofacial pains resembling presentations of primary headaches' as in ICOP.[19]

All patients gave consent to use their individual anonymized data for research purposes. Ethics approval for the study was provided by National Research Ethics Service Committee, London Dulwich (No. 15/L0/1108).

2.1 | Axis-II/IMPARTS data

Integrating Mental and Physical Healthcare: Research Training and Services (IMPARTS) is a web-based screening system implemented by Kings College Hospital to routinely screen and collect data covering various aspects of physical and mental health outcomes from a number of self-report standardized questionnaires. IMPARTS/Axis-II data from patients were extracted and integrated with Axis-I/Clinical data. The integrated data were anonymized and utilized for this research.

2.2 | Measures of sleep, pain and psychological functions

Sleep was measured using the Chronic Pain Sleep Inventory (CPSI). CPSI consists of 5 items rated on 0-100 mm VAS assessing: trouble falling asleep due to pain (CPSI1), the need for sleep medication (CPSI2), awakening by pain during the night (CPSI3) and in the morning (CPSI4) and overall sleep quality (CPSI5). Psychometric testing supports the reliability and validity of using an abbreviated single index attributing sleep problems to pain (mean of CPSI1, CPSI3 and CPSI4), the Sleep Problem Index (SPI).[21] SPI has high factor loadings (>80%) and a high internal consistency (>90%).[21]

Pain severity and pain interference experienced in the last 7 days were assessed using Facial Pain Brief Pain Inventory (FPBPI). Psychometric testing of FPBPI has supported the reliability and validity of this measure in facial pain such as trigeminal neuralgia (TN).[22] Patients were asked to rate their pain or interference on an

11-point scale, where 0 is 'no pain'/'does not interfere' and 10 is 'pain as bad as you can imagine'/'completely interferes'.

Somatic symptom burden in OFP was assessed using a shortened version of Patient Health Questionnaire-15 (PHQ-15).[23] PHQ-15 is a reliable validated questionnaire used in clinical and occupational healthcare settings.[23–25] The ordinal frequency response categories for 13 items (symptom) ranged from 0 ('not bothered at all') to 2 ('bothered a lot') with a total score range of 0–26.

Depression and anxiety were measured using PHQ-9 and GAD-7, respectively. PHQ-9 is a well-validated and widely used screening and severity measure for depression symptomatology in primary care and physically ill populations in secondary care.[26] GAD-7 is a reliable and valid measure of anxiety in primary care, secondary care and the general population.[27] On both scales, items were scored on a 4-point scale ranging from 'not at all' (0) to 'nearly every day' (3) with a total score range of 0–27 for PHQ-9 and 0–21 for GAD-7. Patients only completed all questionnaire items if they responded affirmatively to either of the initial two items (i.e. scored ≥ 2). All patients were also asked to indicate if they recently experienced a stressful life event. The response was binary, with 'yes' or 'no'.

The severity of chronic pain or the way it interferes with their daily functioning in the last 6 months was assessed using the 7-item Graded Chronic Pain Scale (GCPS).[28] This instrument provides a score that enables chronic pain patients to be classified into four hierarchical categories, according to their pain severity or interference.

2.3 | Statistical analysis

Comparisons of sleep problems, sleep quality and need for sleep medication between OFP diagnostic groups were made using analysis of variance (ANOVA) and χ^2, with (post hoc) pairwise *t*-tests administered where significant group differences were observed. Univariate associations between SPI scores and demographic factors, clinical comorbidities, pain severity and pain- and psychological-related function were measured using *t*-tests and Pearson correlation coefficients or Spearman's Rho depending on data distribution. Multivariate associations were calculated using generalized linear models (GLM) with linear links and included only those variables that were significantly related in univariate association analyses. The magnitudes of effects in multivariate analyses were described by unstandardized (B) and standardized (β) beta values, with 95% confidence intervals (CI) provided for the former. Where continuous data in univariate and multivariate analyses did not follow a Gaussian distribution, bias-corrected and accelerated bootstrapping (based on 2000 bootstrap samples) was used to determine CI (of mean differences or beta values) and associated *p* values. Across analyses, the criterion for statistical significance was set at $p < .05$. Statistical analyses were completed with SPSS (IBM, Version 27.0).

3 | RESULTS

3.1 | Demographics and primary diagnosis

Most patients were female (334, 72.6%) with a wide range of ages (18–90 years), averaging just under 50 years old (mean = 48.20 years, SD = 15.30). Time since symptom onset varied from 1 month to 30 years, with a median of 18 months (inter-quartile range = 7.0–54.0). Almost all patients with an available time of onset information (345, 94.5%) had experienced OFP symptoms for 3 months or longer. The primary diagnosis (as per ICOP) of patients presenting at the multidisciplinary OFP clinic is shown in Table 1. Almost 30% presented with pain attributed to a lesion or disease of the orofacial nerves; many of these had post-traumatic trigeminal neuropathic pain (PTNP), a specialty of the clinic. Over a quarter of clinic patients were diagnosed with primary TMD, more than half of these presented with myofascial OFP only while a quarter exhibited both myofascial and temporomandibular joint (TMJ) pain. A smaller number (76) were diagnosed with primary headaches presenting in the orofacial region, predominantly migraine, while 59 patients presented with OFP attributed to disorders of dentoalveolar and anatomically related structures. Idiopathic OFP was less frequently diagnosed ($n = 28$), but when it was, it almost always was Burning Mouth Syndrome (BMS).

3.2 | Sleep problems in OFP

Seventy-three (15.9%) patients responded 0 on all CPSI items, indicative of invalid responding, and were excluded from analyses concerning sleep. Of the 387 patients with valid data (Table 2), sleeping problems were, on average, of mild severity (SPI mean = 31.87) with high internal consistency across the three SPI items (Cronbach's alpha = 0.90). All but 60 patients (327 or 84.5%) had an SPI score of >0 indicating some pain-related sleep disturbances (27.1% scored >50); 77.0% indicated that they had trouble falling asleep at least some time (i.e. scored >0), whereas 73.6% and 72.9% reported being awakened by pain in the night and in the morning, respectively, on one occasion or more. The overall quality of sleep was close to the mid-point (mean = 51.34) while almost half indicated requiring the use of sleep medication to fall asleep at least sometimes (approximately 1 in 5 patients indicated they did so often).

3.3 | Pain severity and pain-related and psychological function in patients with OFP conditions

According to the BPI questionnaire, mean 7-day average pain levels were moderate (Table 2), although a quarter (106, 24.8%) of patients reported experiencing (on average) severe pain (≥7).[29] The mean pain interference was 3.54 (Table 2). The prevalence of somatization

TABLE 1 Prevalence of orofacial conditions seen at multidisciplinary orofacial pain clinic (KCH) between Jan 2019 and Feb 2020.

Code	Diagnosis	*n*	*n* (%)
1	Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures		***59 (12.8%)***
1.1	Dental pain (Dent P)	44	
1.2	Oral mucosal, salivary gland and jaw bone pain (Muc P)	15	
2/3	Painful Temporomandibular disorders (TMD)		123 (26.7%)
2	Myofascial orofacial pain with no TMJ pain (Myofascial only)	66	
3	Temporomandibular joint (TMJ) pain with no myalgia (TMJ pain only)	26	
2&3	Myofascial orofacial pain and TMJ pain (Myofascial & TMJ pain)	31	
	Non-painful temporomandibular disorders	2	2 (0.4%)
4	Orofacial pain attributed to lesion or disease of the cranial nerves		134 (29.1%)
4.1	*Pain attributed to lesion or disease of trigeminal nerve*		
4.1.1	Trigeminal neuralgia (TN)	27	
4.1.2	Other trigeminal neuropathic pain (OTNP)	107	
4.1.2.1	Trigeminal neuropathic pain attributed to herpes zoster	1	
4.1.2.2	Trigeminal post-herpetic neuralgia	1	
4.1.2.3	Post-traumatic trigeminal neuropathic pain	81	
4.1.2.3.1	Probable post-traumatic trigeminal neuropathic pain	16	
4.1.2.4	Trigeminal neuropathic pain attributed to other disorders	5	
4.1.2.4.1	Probable trigeminal neuropathic pain attributed to other disorders	2	
4.1.2.5	Idiopathic trigeminal neuropathic pain	1	
4.2	*Pain attributed to lesion or disease of glossopharyngeal nerve*		
	Non-painful trigeminal neuropathy		7 (1.5%)
	Post-traumatic trigeminal neuropathy	7	
5	Primary headaches presenting in the orofacial region		76 (16.4%)
5.1	Migraine presenting in the orofacial region (Migraine)	58	
5.2	Tension-type presenting in the orofacial region		
5.3	Trigeminal autonomic cephalgia presenting in the orofacial region (TAC)	17	
5.4	Neurovascular orofacial pain	1	
6	Idiopathic orofacial pain		28 (6.1%)
6.1	Burning mouth syndrome (BMS)	25	
6.2	Persistent idiopathic facial pain (PIFP)	1	
6.3	Persistent idiopathic dentoalveolar pain	2	
7	Others (functional neuropathy, non-painful conditions, yet to be diagnosed)		31 (6.7%)
	Total		460

syndromes at a moderate-to-high level was 36.9%, markedly higher than that observed in a normative (non-clinical) study.[30] Most patients screened negatively on the PHQ-9 and GAD-7, but 19.3% and 22.2% reported depression and anxiety symptom levels that were moderate-to-severe (≥10), respectively. Additionally, more than a third of patients reported recently experiencing a stressful event.

3.4 | Sleep problems according to primary OFP diagnosis

Sleep problem index (SPI) scores differed across major diagnostic groups [Figure 1; $F(4,361) = 5.30$, $p < .001$]. Post-hoc pairwise comparisons suggested that patients with primary headache (presenting in the orofacial region) classifications experienced significantly greater sleep difficulties than patients with painful TMD (mean difference = 13.54, CI = 4.63, 22.45), OFP attributed to lesion or disease of the cranial nerves (mean difference = 20.22, CI = 11.87, 28.80) and idiopathic OFP (mean difference = 17.30, CI = 2.60, 31.72). Within each of the 3 largest diagnostic groups, only the difference in SPI scores between patients with migraine and patients with trigeminal autonomic cephalgia (TAC)/other neurovascular orofacial pain was significant (Figure 1B; mean difference = 22.43, CI = 6.10, 38.77).

In contrast, overall sleep quality was comparable across major diagnostic groups [Figure 2; $F(4,361) = 0.75$, $p = .557$]. Nevertheless, the reported need for sleeping medication to fall asleep did differ across groups [Figure 2B; X^2 (8)=23.63, $p = .003$], reflecting a greater propensity for patients with primary headaches to report using sleep

TABLE 2 Sleep, pain severity and interference, psychological function and pain-related disability in patients with OFP conditions.

	Mean (SD)
Sleep function (CPSI; $n=387$)	
Sleep problem index (0–100)	31.87 (30.27)
Trouble falling asleep because of the pain	33.11 (32.57)
Awakened by pain during the night	31.58 (33.27)
Awakened by pain in the morning	30.92 (33.41)
Overall sleep quality (0–100)	51.34 (28.59)
Use of sleep medication	*n* (%)
Never (i.e. 0)	195 (50.4)
Occasionally/Sometimes (i.e. 1–49)	108 (27.9)
Frequently/Always (i.e. 50–100)	84 (21.7)
Pain severity (FPBPI; $n=427$))	
Pain now (0–10)	3.61 (2.92)
Strongest pain (0–10)	5.30 (3.07)
Average pain (0–10)	4.39 (2.80)
Pain interference (FPBPI; $n=427$; 0–10)	3.54 (2.70)
Somatization (PHQ-15; $n=436$)	7.52 (5.48)
	n (%)
Minimal (0–4)	114 (26.1)
Low (5–9)	161 (36.9)
Medium (10–14)	83 (19.0)
High (≥15)	78 (17.9)
Depression (PHQ-9; $n=441$)	
None (Negative screen/0–4)	344 (78.0)
Mild (5–9)	12 (2.7)
Moderate (10–14)	29 (6.6)
Moderately to Severe (15–19)	27 (6.1)
Severe (≥20)	29 (6.6)
Anxiety (GAD-7; $n=442$)	
None (Negative screen/0–4)	321 (72.6)
Mild (5–9)	23 (5.2)
Moderate (10–14)	48 (10.9)
Severe (15–21)	50 (11.3)
Recent stressful event (IOES; $n=422$)	148 (35.1)
Graded Chronic Pain Scale ($n=419$)	
No facial pain (last 6 months)	37 (8.8)
Grade I—Low disability/Low intensity	144 (34.4)
Grade II—Low disability/High intensity	107 (25.5)
Grade III—High disability/Moderately limiting	64 (15.3)
Grade IV—High disability/Severely limiting	67 (16.0)

Note: Two items were excluded from the original PHQ-15 scale: 'menstrual cramps or other problems with your periods' (applying only to female participants) and 'pain or problems during sexual intercourse'; the continuous score is the raw sum of the 13 items while the classifications represent pro-rata scoring of 13 items to reflect that of 15 items (i.e. score from the 13 items were imputed to the other 2 items) applied to standard cut-offs.

Abbreviations: CPSI, Chronic Pain Sleep Inventory; FPBPI, Facial Pain Brief Pain Inventory; GAD-7, General Anxiety Scale-7; IOES, Impact of Event Scale; PHQ-15, Patient Health Questionnaire-15; PHQ-9, Patient Health Questionnaire-9.

medication to fall asleep relative to each of the other major diagnostic OFP groups.

3.5 | Sleep problems according to demographic characteristics, pain severity and interference and psychological function

Sleep problems were more marked in female patients and there was a small but reliable positive association with the duration of OFP condition (Table 3). Patients with secondary diagnoses of TMD and/or migraine/headache also had more sleep problems than those without. Pain severity, pain interference and somatization levels were moderately correlated with SPI scores, indicative of worse sleep in those with greater pain, more pain-related interference with daily activities and higher somatization levels. The small proportions of patients indicating moderate-to-severe depression and moderate-to-severe anxiety (≈20%) also reported significantly elevated SPI scores relative to those without or with mild depression and without or with mild anxiety, respectively (for each, differences were, on average, >20 points). Finally, patients who reported recently experiencing a stressful event also indicated significantly greater sleep problems.

Supplementary analyses revealed significant differences across (major) diagnostic groups with respect to average pain severity, pain interference, somatization levels and proportion with moderate/severe depression (Table S1, for all comparisons $p<.029$), reflecting the greater OFP burden on patients with primary headache disorders. Given the covariance of diagnosis (presence of headache disorder) and these factors, and covariance of pain characteristics and affective function with sleep problems (and likely covariance with each other), multivariate analyses were warranted to better determine the factors that are independently associated with sleep problems in patients with OFP conditions.

The results of the multivariate regression model examining the relationship between SPI scores and the demographic, clinical, pain-related and psychological factors evidencing a significant association in univariate analyses are shown in Table 4. Pain interference was the strongest correlate, with a more than 4-point change in SPI score per point increase. Average pain severity also remained highly significant with an almost 3-point change in score per point increase on the pain VAS. There were also significant independent associations of sleep problems with somatization levels and reported recent experiences of a stressful event. While the presence of a primary headache disorder increased SPI scores by 5.63 points, it failed to achieve statistical significance in the model, suggesting the impact of primary headache on sleep problems may be partly accounted for by increased pain severity and greater levels of pain interference specific to headache disorders. The *n* value of the model was 325 due to missing data regarding the onset time of the OFP condition ($n=62$). However, when the multivariate model was readministered excluding 'duration' of the OFP condition (i.e. with the larger sample), average pain severity,

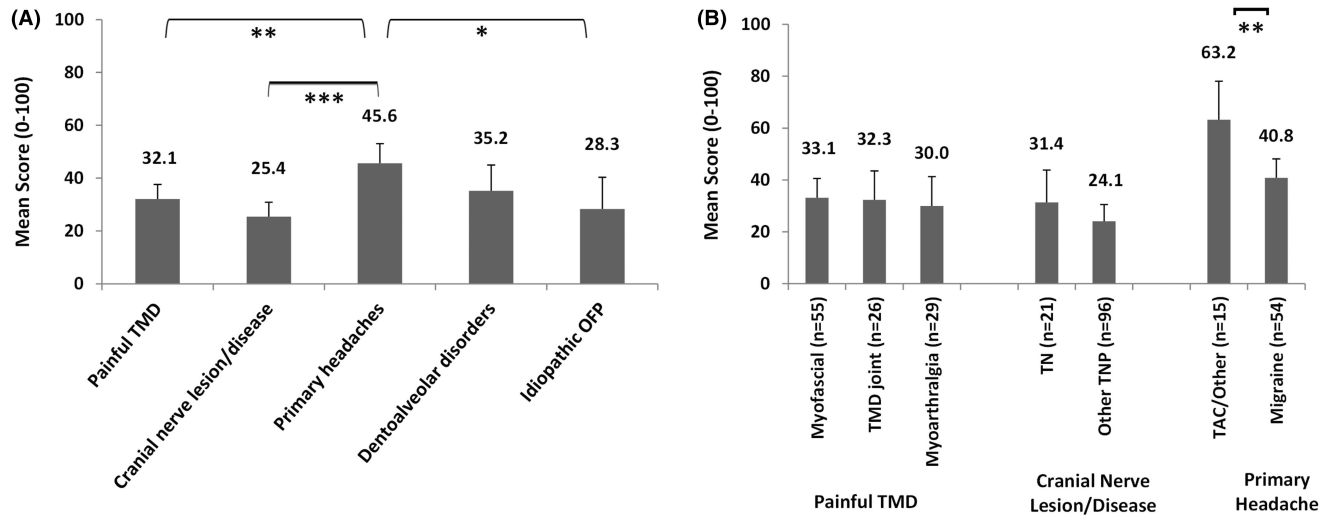

FIGURE 1 Sleep problem index according to orofacial pain (OFP) diagnosis (A) and (sub)diagnosis within painful temporomandibular disease (TMD), orofacial pain attributed to lesion or disease of the cranial nerves and primary headaches presenting in orofacial region classifications (B). Higher scores on the sleep problem index indicate greater problems. TAC, trigeminal autonomic cephalgias; TMD, temporomandibular disorders; TN, trigeminal neuralgia; TNP, trigeminal neuropathic pain. Value labels are mean scores. Error bars represent 95% confidence intervals. Asterisks indicate significant differences between (sub)diagnostic classifications (*$p < .05$, **$p < .01$, ***$p < .001$).

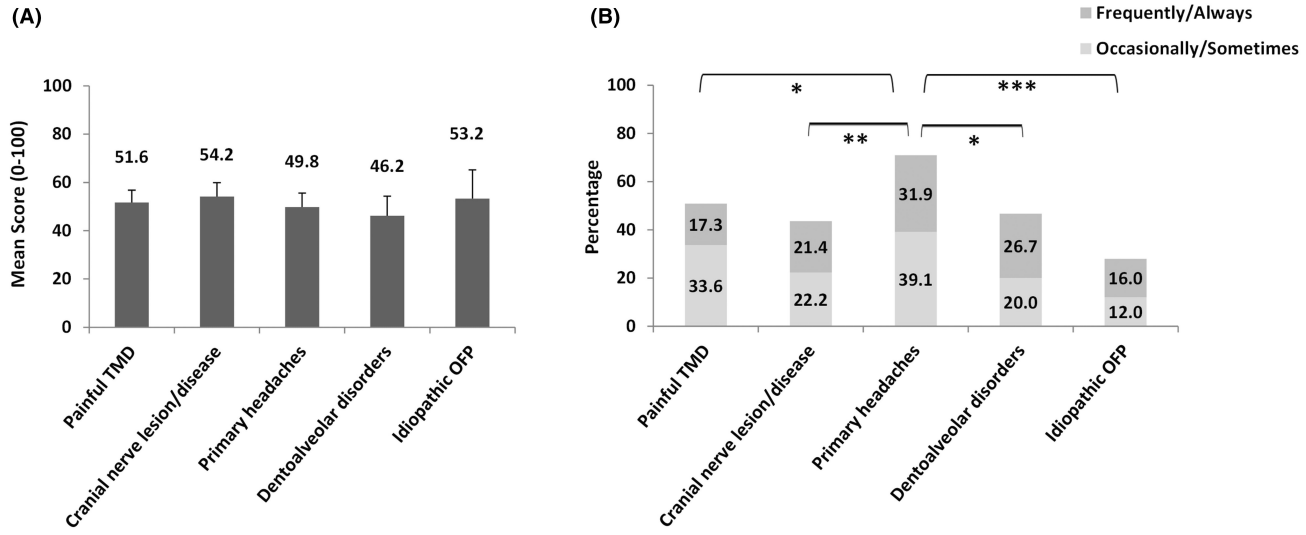

FIGURE 2 Mean overall sleep quality (A) and percentage indicating the need for sleeping medication to fall asleep (1–50 and 51–100 on 0–100 VAS were considered 'Occasionally/Sometimes' and 'Frequently/Always', respectively) (B) according to orofacial pain diagnosis. Higher scores on sleep quality indicate better sleep. Value labels are mean scores (A) and percentages (B). Error bars represent 95% confidence intervals. Asterisks indicate significant differences between diagnostic classifications (*$p < .05$, **$p < .01$, ***$p < .001$).

pain interference and somatization score remained significant correlates, although experiencing a recent stressful event failed to achieve significance ($p = .067$; see Table S2).

4 | DISCUSSION

This study is one of only a handful that has examined pain-related sleep problems across a range of OFP conditions. We found the presence of any sleep disturbances due to pain in more than 85% of our OFP sample and marked sleep problems in more than a quarter (27.1%). Our findings are broadly in line with that of Sun et al.'s[31] recent meta-analysis of 20 chronic pain studies (including body pain) which reported a pooled prevalence of sleep disturbances of 75.3% using Pittsburg Sleep Quality Index (PSQI) cut-offs and 72.9% using Insomnia Severity Index (ISI) cutoffs. They are also consistent with that of a recent sleep and OFP review which noted poor sleep quality in patients with BMS, TN, PTNP and TMD compared to healthy participants.[32] Insomnia has been reported in 37% of patients seeking care at the orofacial pain unit at the University of Zurich.[10] Similarly,

TABLE 3 Associations between sleep problems with demographic factors, clinical comorbidities, pain severity and pain- and psychological-related function in patients with OFP conditions ($n = 387$ unless otherwise stated).

	Sleep problem index (0–100)			
	***r* (95% CI)**	***p***		
Age	−0.01 (−0.11, 0.09)	.875		
Duration (months; $n = 325$)	**0.17 (0.06, 0.28)**	**.002**		
Average pain severity	**0.61 (0.54, 0.67)**	**<.001**		
Pain interference	**0.64 (0.58, 0.70)**	**<.001**		
Somatization score	**0.46 (0.37, 0.53)**	**<.001**		
	Mean (SD)	Mean (SD)	Mean diff. (95% CI)	*p*
Gender	Male ($n = 105$)	Female ($n = 282$)		
	21.82 (27.19)	**35.62 (30.54)**	**13.80 (7.04, 20.76)**	**<.001**
Comorbid TMD or Migraine/ Headache	No ($n = 318$)	Yes ($n = 69$)		
	29.77 (30.07)	**41.55 (29.48)**	**11.78 (3.96,19.60)**	**.003**
Comorbid body pain or sleep disease	No ($n = 371$)	Yes ($n = 16$)		
	31.22 (29.97)	47.04 (34.09)	15.83 (−1.49,33.08)	.059
Depression	None/Mild ($n = 311$)	Mod/Severe ($n = 76$)		
	27.08 (28.00)	**51.45 (31.46)**	**24.37 (17.15, 31.59)**	**<.001**
Anxiety	None/Mild ($n = 301$)	Mod/Severe ($n = 86$)		
	27.41 (27.80)	**47.49 (33.39)**	**20.08 (12.28, 27.88)**	**<.001**
Stressful event	None recently ($n = 251$)	Recent ($n = 136$)		
	28.02 (28.30)	**38.97 (32.52)**	**10.95 (4.43, 17.47)**	**.001**

Note: 'Sleep problem index' from the Chronic Pain Sleep Inventory; 'Average pain severity' (7-day) and Pain interference (7-day; excluding sleep item) from Facial Pain Brief Pain Inventory; 'Somatization score' from Patient Health Questionnaire-15 (excluding sleep item); 'Depression' from Patient Health Questionnaire-9; 'Anxiety' from Generalized Anxiety Disorder-7; 'Stressful event' from Impact of Event Scale. *p* values were calculated from Pearson r/Spearman's rho and independent groups t-tests considering all OFP patients (significant associations are emboldened).

Abbreviations: Mean diff., mean difference; TMD, temporomandibular disorder(s).

a sleep questionnaire-based study conducted with more than 3000 patients with predominantly TMD diagnosis reported significant associations between sleep deprivation and OFP.[33] The average pain intensity was similar to the current study, but the sleep indices were varied (5% took medication for sleep vs 50% in the present study). It is possible to sleep problems were more prevalent in our TMD cohort than that of Lee et al.[33]

Sleep problems were greater in patients presenting with primary headaches in the orofacial region, particularly TACs. However, OFP patients with neurovascular pain often present with higher pain levels and have more bodily complaints,[16] and once the level of experienced pain intensity was accounted for, the presence of primary headache disorder was not a significant correlate of pain-related sleep disturbances.

The finding that sleep problems are independently associated with pain intensity is consistent with previous reports from a more heterogenous group of patients with chronic pain[6] (more than 10% with head pain); patients with CLBP[7] and OFP.[9] While the link between pain and sleep is clear, the directionality is often debated. Decades of discovery from OPPERA study suggest changes in sleep quality precede the onset of TMD.[11]

Sleep problems have negative effects on pain-related health outcomes including interference from pain.[4] Among chronic pain patients, Campbell et al.[34] observed a significant association between increased sleep disturbances and increased pain interference. Our findings in this chronic OFP cohort support previous work,[6–8] with interference from the pain associated with an elevated risk of sleep problems independently of pain intensity. However, in contrast to the TMD study by Dubrosky et al.[12] we did not find a significant independent association between anxiety/depression and sleep in multivariate models despite overwhelmingly significant relationships in univariate analyses. This suggests that pain intensity and interference which tend to be higher in depressed and anxious OFP patients may better account for sleep difficulties in this group. In a recent study of sleep in TMD, Lee et al.[33] noted the challenges of determining what causes sleep problems and whether it is pain or associated psychological distress that drives poor sleep.

The significant positive association in the current study between sleep problems and somatic complaints is in line with the results of other studies using different instruments and different populations.[14] It is possible that sleep problems/disturbances may be a factor in the persistence and aggravation of somatic complaints irrespective of anxiety and depression. In future, longitudinal studies should address the relationship between sleep problems and specific somatic complaints in OFP patients.

TABLE 4 Multivariate associations of sleep problems with demographic factors, clinical comorbidities, pain severity and pain- and psychological-related function in patients with OFP conditions ($n = 325$).

	Sleep problem index (0–100)			
Variables	**B**	**CI B**	***β***	***p***
Female gender	3.42	−1.66,8.79	0.05	.219
Duration (months)	0.03	−0.01,0.07	0.06	.151
Primary headache diagnosis	5.63	−1.83,13.14	0.08	.105
Comorbid TMD or Migraine/ Headache	1.38	−4.82,7.36	0.02	.653
Average pain severity	**2.90**	**1.69,4.12**	**0.26**	**<.001**
Pain interference	**4.16**	**2.93,5.44**	**0.36**	**<.001**
Somatization score	**0.90**	**0.17,1.63**	**0.14**	**.016**
Moderate/Severe depression	−3.12	−12.40,6.60	−0.04	.532
Moderate/Severe anxiety	−0.96	−9.59,7.95	−0.01	.835
Recent stressful event	**5.81**	**0.93,10.87**	**0.09**	**.030**

Note: 'Sleep problem index' is from Chronic Pain Sleep Inventory; 'Average pain severity' (7-day) and Pain interference (7-day; excluding sleep item) were from Facial Pain Brief Pain Inventory; 'Somatization score' from Patient Health Questionnaire-15 (excluding sleep item); 'Moderate/Severe Depression' from Patient Health Questionnaire-9; 'Moderate/Severe Anxiety' from Generalized Anxiety Disorder-7; 'Recent stressful event' from Impact of Event Scale. Model only included variables, where a significant association (i.e. $p < .05$) was observed in univariate analyses; Reference categories for Gender = Male, Primary headache diagnosis = No primary diagnosis of headache; Comorbid Temporomandibular Disorder(s) (TMD) or Migraine/Headache = No comorbid condition, Moderate/Severe depression = None/Mild depression, Moderate/Severe anxiety = None/Mild anxiety, Recent stressful event = No recent stressful event. Average pain severity, Pain interference and Somatization scores and Duration were continuous variables (as such, beta values represent a change in (sleep) score per point increase or per month increase). For 'Sleep problem index' omnibus, $F = 27.97$, $p < .001$, Adjusted $R^2 = 0.45$; associations with significance $p < .05$ are indicated in bold.

Abbreviations: B, unstandardized beta; CI, 95% confidence interval; β, standardized beta.

Our findings illustrate that recent stressful events are associated with sleep problems independently of pain severity, interference and affective function in line with previous work suggesting an important role of stressful or adverse events in the development of sleep problems[17,18] (although no research has examined the probability of traumatic event secondary to sleep problems).[18] Sleep disturbances are considered common after exposure to stressful life events. This raises the question of whether OFP may render some individuals vulnerable to sleep difficulties and whether a stressful event can serve as a precipitant of these problems.

Interestingly, there was a lack of association between gender and sleep problems in multivariate models although univariate analyses suggested females experienced greater sleep difficulties than males. It is possible that there is no specific relationship or relationship that is not better accounted for by pain severity and other important factors in relation to gender and sleep in orofacial pain. It may be dependent on multiple aspects like age, pain or medical comorbidity and hormonal factors are an essential part of phenotyping the patient.

There are several mechanisms hypothesized to mediate the effects of sleep deficiency on pain. A review by Haack[35] provides neurobiological evidence to support mechanisms likely to be involved in pain modulation by sleep loss. Specifically, loss of sleep may have a deactivating effect on several systems/mediators with analgesic properties, including the opioid system, the orexinergic system, the melatonin system and dopamine signalling and, at the same time, activate systems/mediators with predominantly hyperalgesic properties, such as nitric oxide and adenosine signalling and inflammatory mediators of the immune system.[35] One factor purported to underlie the interplay of sleep and pain (linked with neurobiological changes) that has recently garnered attention is circadian rhythm disruption (CRD).[36,37] The circadian system is a fundamental biological process that coordinates rhythms in physiology and behaviour to the 24-h light–dark cycle.[38] Regulation of sleep-wake cycle, secretion and release of hormones, neurotransmitters involved in nociception are under the tight control of circadian rhythms.[39] Their disruption is proposed to play a common psychopathological role across multiple mental health disorders[40] and is linked with altered (circadian) expression of genes involved in pain regulation, such as opioid and melatonin receptors.[37] Recent reviews show coarse CRD such as sleep disturbances is frequently present across mental health disorders and further affirms the link between CRD and psychological distress.[38,40] While sleep impairment and chronic pain can predispose patients to psychological distress (through an independent association),[13] circadian system misalignment may affect sleep as well as psychological function associated with pain complaints.[37,40] Future treatments targeting

those core circadian genes associated with the regulation of sleep and pain[41] may better help attenuate sleep and mental health problems in individuals with chronic orofacial pain.[37]

There are some limitations to the present study. Data on sleep were limited to self-report scale-based measures with an invalid response rate of about 15%. Additionally, although the CPSI assesses areas of sleep most relevant to pain, and 85% reported some degree of sleep disturbances due to pain, it is limited in scope[21] and possibly underestimates global sleep conditions in these populations. For example, insomnia, disordered sleep breathing or their co-occurrence (Co-morbid Insomnia and Sleep Apnoea; COMISA) are highly prevalent in OFP[42] with significant impacts on the sleep–pain interaction but cannot be accurately assessed with this tool. Furthermore, the relationship between obstructive sleep apnoea (OSA; with components of sleep fragmentation and hypoxaemia) and pain sensitivity may be more complex. Insomnia/sleep fragmentation and intermittent hypoxemia are reported to have opposite effects on pain sensitivity; insomnia increases pain sensitivity but intermittent hypoxaemia decreases it.[43,44] This sleep–pain interface in patients with OSA/COMISA is further complicated by potential interaction with patients' psychosocial distress, all of which maybe be influenced by and from circadian timing responses. Also, other potentially key (sleep-related) variables such as cognitive pre-sleep arousal were not assessed here. Future work using measures like sleep diaries or objective sleep markers will likely provide richer data about sleep problems and how they arise in OFP.

The present study was also limited by the screening procedures to assess psychological-related factors of anxiety (GAD-7) and depression (PHQ-9), which necessarily entailed a loss of information and could have reduced the power to detect significant correlates in univariate and multivariate analyses. Finally, as this is a cross-sectional study, we cannot derive causal conclusions about the relationship between sleep problems and other factors. Additional work using a longitudinal design exploring the association of sleep with demographic factors, clinical comorbidities, recent stressful events, pain severity and pain- and psychological-related function within specific orofacial pain groups and subgroups would be beneficial.

5 | CONCLUSION

Sleep problems are greater in patients with primary headaches presenting in the orofacial region than OFP conditions, but the magnitude of this difference decreases once pain severity and other pain-related and psychological factors are controlled for. Both pain severity and interference from pain are independently associated with sleep problems with the latter being the strongest correlate. Our study in this OFP cohort highlights the importance of assessing somatic complaints and recent stressful life events in individuals with sleep and pain conditions, irrespective of other mental comorbidities. Treating circadian rhythm misalignment and thereby establishing circadian rhythms can be a potential avenue for managing multiple factors influencing and influenced by sleep–pain interaction.

AUTHOR CONTRIBUTIONS

Tara Renton, Jared G. Smith and Priya Thimma Ravindranath: design of the study. Priya Thimma Ravindranath and Candice Ebelthite: collection of data. Jared G. Smith and Priya Thimma Ravindranath: performing all analysis, interpretation of results and writing the manuscript. Tara Renton, Jared G. Smith, Niloofar and Rasooli Nia: interpretation of results and critical revision of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

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