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Obstructive sleep apnea is common in patients with high-impact chronic pain – an exploratory study from an interdisciplinary pain center

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Abstract

Background: Sleep disturbances are increasingly recognized as a major part of chronic pain pathology. Obstructive sleep apnea (OSA) is a common occurrence in patients with chronic pain attending specialized pain clinics, yet its prevalence remains unclear. Using screening tools such as the Berlin and STOP-BANG questionnaires may aid in early identification of OSA and improve clinical care. This study i) examined the frequency of OSA based on objective sleep monitoring in patients with high-impact chronic pain, ii) explored potential differences in self-reported pain and sleep characteristics between patients with and without OSA, and iii) tested the agreement between OSA classification based on objective assessment and two OSA screening questionnaires.

Methods: A consecutive cohort of 90 patients (71 women and 19 men; mean age: 47.1±11.0 years) referred for interdisciplinary pain treatment, underwent one night of sleep monitoring using portable respiratory polygraphy (RP), and suspected OSA was confirmed with polysomnography (PSG). Self-reported data on clinical pain (severity, pain drawings and health-related quality of life), sleep characteristics (sleep quality insomnia, sleepiness), and risk of OSA (Berlin and STOP-BANG questionnaires) were collected the day before RP assessment.

Results: Forty-six (51.1%) patients were classified with OSA according to RP and verified with PSG. Twenty-eight patients (31.1%) had moderate or severe OSA (apnea-hypopnea index [AHI] >15). Patients with OSA reported lower sleep quality compared with patients without OSA. Scores on pain severity, disability, quality of life, insomnia and sleepiness were comparable between patients with and without OSA. Sensitivity and specificity were 78.6% and 45.2% respectively for the Berlin questionnaire, and 71.4% and 58.1% respectively for the STOP-BANG questionnaire. The agreement for both questionnaires with objective assessment was poor-to-fair. Both

questionnaires had acceptable negative predictive values but low positive predictive values reducing the clinical utility to identify patients with low OSA-risk in this sample.

Conclusion: The current study demonstrates a high prevalence of OSA in patients with high-impact chronic pain referred to specialized pain treatment, however the clinical pain profiles were similar in patients with and without OSA. The Berlin and STOP-BANG questionnaires have poor specificity and low-to-fair agreement with RP/PSG questioning their clinical utility in identifying OSA in this sample.

Keywords: Sleep, chronic pain, OSA, respiratory polygraphy, STOP-BANG, Berlin

1. Introduction

Chronic pain, recognized by the International Association for the Study of Pain (IASP) as pain that persists longer than 3 months [1], remains a major societal challenge given its contribution to years lived with disability [2]. Several lines of evidence have shown associations between a variety of chronic pain conditions and psychological factors such as pain catastrophizing [3], depression [4], and anxiety [5]. However, a recent systematic review highlighted the need for a better understanding of underlying factors for chronic pain [6]. Earlier evidence has demonstrated that partial [7] and total sleep deprivation [8] may affect central pain mechanisms, indicating that regular sleep is important to maintain a healthy response to pain. Indeed, a frequent complaint in chronic pain is disturbance of sleep, where an estimated 66-88% of patients with chronic pain report low-quality sleep [9–11]. While a recent review on polysomnographic findings in nonmalignant chronic pain, reported a non-consistent pattern of objective sleep disturbances [12], recent meta-analyses [13,14] reported that chronic pain and fibromyalgia patients experience sleep disturbances involving sleep initiation and maintenance. Other studies have shown that sleep disturbances plays a pivotal part in chronic pain pathology [15,16]. For instance, a recent machine learning study on 277 patients undergoing tertiary pain management, demonstrated that patients with severe pain were often characterized as having sleep problems along with more pain areas, greater affective pain interference, fear of pain, and lower self-rated health [17]. In this respect, sleep disordered breathing (SDB) is a prevalent sleep problem that has been reported as high as 32-82% in women with fibromyalgia [18,19]. Obstructive sleep apnea (OSA) is the most common type of SDB. OSA is clinically characterized by excessive daytime sleepiness, insomnia, fatigue or decreased quality of life [20,21] and is diagnosed by sleep recordings - respiratory polygraphy (RP) or polysomnography (PSG) - quantifying apneas and hypopneas per hour in the apnea-

hypopnea index (AHI). In an elderly population it was shown that subjects diagnosed with OSA also exhibited increased pain sensitivity [22]. It therefore seems evident that sleep and pain are intimately linked, and even if concurrent treatment of pain and sleep impairment is warranted, this is rarely done in a systematic manner [23]. Traditionally, sleep disturbances in patients with chronic pain have been based on self-reported questionnaires on e.g. poor, non-restorative sleep with multiple nightly awakenings [10,24], whereas the current gold-standard for assessing sleep disturbances is polysomnography as is utilized in e.g. OSA [25]. However, since PSG requires technical prowess and is expensive to utilize [26,27], the clinical implementation for assessment of SDB in patients with chronic pain presents a challenge, even if screening for e.g. OSA may be relevant in this population [9]. Further, it remains unclear if OSA screening questionnaires such as the Berlin [28] and the STOP-BANG [29] questionnaires may inform on OSA presence in agreement with objective findings in chronic pain patients. [12].

Therefore, the current study aimed to explore the frequency of OSA based on objective sleep monitoring in patients with high-impact chronic pain, defined as persistent pain with substantial restriction of life activities lasting 6 months or more [30], referred for interdisciplinary pain treatment. Secondary aims were to identify possible differences in clinical pain characteristics between patients with and without OSA, and to determine the agreement in classification of OSA between the objective assessment and two OSA screening questionnaires (the Berlin questionnaire and the STOP-BANG questionnaire). Based on earlier evidence we hypothesized (1) high prevalence of OSA in the current sample; (2) patients with OSA would present with worse clinical characteristics when compared to no-OSA patients; and (3) that subjective questionnaires (Berlin and STOP-BANG) would show high agreement with objective OSA classification [28,31].

2. Methods and materials

2.1 Patient population

Patients between 18-65 years of age referred for interdisciplinary pain treatment at the University Hospital Pain Center in Odense, Denmark between January and December 2017, were included as part of the everyday clinic. Exclusion criteria were inability to understand Danish and currently undergoing treatment for sleep apnea. All patients referred to the Pain Center have chronic (> 6 months) non-cancer pain conditions and have previously tried a number of treatments in primary and secondary care settings with an unsatisfactory clinical response. Patients in this setting have moderate to severe pain intensity, high disability, and psychological distress, and most report pain in more than one body area [32–34]. This exploratory and observational cohort study was registered and approved by the local ethics committee (S-20160129) and The Danish Data Protection Agency and was conducted in accordance with the Declaration of Helsinki.

2.2 Procedure

During the initial visit to the Pain Center, patients were informed about the study. Patients who consented to participate were scheduled for a clinical examination on a separate day. At this visit patients completed the questionnaires and underwent a clinical examination. Hereafter, patients were instructed how to use the sleep monitoring device, and underwent one night of sleep monitoring the following night.

2.3 Monitoring of obstructive sleep apnea

To evaluate the presence of OSA, all patients underwent one night of sleep monitoring with a portable RP sleep device (NOX T3^{TM}, NOX Medicals, Iceland). RP is an accepted modality for

diagnosing OSA by the 3rd edition of the International Classification of Sleep Disorders (ICSD-3) [35]. The NOX T3™ was originally validated for detecting OSA by assessing airflow (cannula pressure transducer), thoracic and abdominal respiratory effort (respiratory inductance plethysmography), wireless pulse oximetry, body position, snoring, actigraphy, and audio, and has good measure agreement with polysomnography (PSG) [36]. Abnormal (AHI > 5) or inconclusive RP results were confirmed by PSG at the Odense University Hospital Respiration Center within approximately 2 weeks after the RP.

2.3.1 Polysomnography

NOX A1 equipment and software from NOX medical version 5.1.3.20388, were used for PSG, and the recording and scoring were performed by trained clinicians in accordance with The American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events, version 2.5 [37]. Six electroencephalogram leads (F3/F4, C3/C4, O1/O2), right and left electro-oculogram, and submental electromyogram were used for sleep scoring. Pressure flow nasal cannula, inductive thoracic and abdominal belts (effort), and oximetry were used for respiratory assessment, and the AASM hypopnea scoring rule 1A was applied (≥ 10 s duration of ≥ 30% of air flow reduction associated with a ≥ 3% decrease in oxygen saturation and/or an electroencephalographic arousal). Apneas were scored when there were a 90% drop in the flow signal lasting 10 or more seconds. The apnea-hypopnea index (AHI) is used to grade the severity of OSA into mild OSA, defined as AHI of 5-15, and moderate-severe OSA defined as AHI ≥15 [38].

2.4 Clinical examination

Prior to sleep monitoring, patients were assessed by a pain specialist from the Pain Center and based on pain distribution and pain history patients were classified into one of the following pain conditions: widespread pain, radiating back/neck pain, neuropathic pain condition or regional/localized pain.

Height, weight, blood pressure, neck circumference, and Mallampati score were measured by a trained nurse. The Mallampati score is categorized in four classes, based on a visual assessment of the distance from the tongue base to the roof of the mouth. A higher class indicating less space, has been associated with higher incidence of OSA [39].

2.5 Questionnaire data

A web-based questionnaire system (PainData) was used to collect data on demographics (sex, age), clinical pain characteristics and sleep (quality, insomnia, sleepiness, risk of OSA) was completed at the hospital prior to the clinical examination [40].

2.5.1 Assessment of pain intensity and health-related quality of life

Peak and average pain intensity during the last 24 hours were assessed on two 11-point numeric rating scales ranging from 0 (no pain) to 10 (worst imaginable pain) [41], which has been shown to be reliable and valid [42]. Furthermore, patients completed pain drawings indicating all locations - divided into 71 body areas - with pain during the previous week [40].

Health-related quality of life (QOL) was assessed using the 0 to 100 Visual Analog Scale (VAS) included in the EuroQol 5-D questionnaire with 100 indicating the best QOL [43].

2.5.2 Sleep-related questionnaires and assessment of risk factors for OSA

Sleep quality was assessed using the four items from the Karolinska Sleep Questionnaire (KSQ) sleep quality subscale, assessing frequency of sleep disturbance, early awakenings, difficulties falling asleep and night time awakenings with difficulty returning to sleep [44,45]. In the Danish version of the KSQ, participants respond using one of 5 categories (1= every night or almost every night, 2= several times a week, 3= several times a month, 4= several times a year, 5= never). The questions and response options used in this study have previously been used to explore sleep difficulties in a large Danish study [46].

Insomnia was assessed with the Insomnia Severity Index (ISI) which encompasses seven items measuring severity of sleep-onset; sleep maintenance and early morning awakening difficulties; satisfaction with sleep patterns; daily function interference; impairments due to sleep problems; and distress or concerns due to sleep problems [47]. Each item is rated from 0-4 (0= no problem, 4= severe problem), yielding a total score of 28, with higher scores reflecting worse insomnia, and is validated for use in research [48] and primary care [49].

Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS). The subjects rate their chance of dozing off or falling asleep in eight different daytime situations, on a 4-point Likert scale (0= would never doze, 3= high chance of dozing). ESS scores greater than 11 is indicative of excessive daytime sleepiness [50].

Risk factors for OSA was evaluated by the Berlin questionnaire and The STOP-BANG questionnaire, which screens for the probability of OSA. The Berlin Questionnaire spans three categories, snoring/gasping; daytime somnolence; and hypertension/BMI. Patients with a positive score in two or more categories are considered at high-risk for OSA [28]. The STOP-BANG questionnaire [31] is a four-item forced yes/no questionnaire which assesses snoring; tiredness, fatigue, or daily sleepiness; external observation of cessation of breathing; and blood pressure, and

is validated in e.g. patients undergoing elective surgery [31], and patients referred to sleep clinics [29]. Three or more positive responses on the questionnaire indicate higher risk of OSA with BMI greater than 35 kg/m^2, age older than 50, male gender, and neck circumference greater than 40 cm greatly increasing the predictive value for OSA [31].

2.6 Statistical analysis

All statistical analyses were performed in SPSS version 24 (IBM Corporation, Armonk, NY). $P < 0.05$ was considered significant, and due to the exploratory nature of the study, p-values were not adjusted for multiple comparisons.

Descriptive data for objective sleep monitoring and questionnaire data on demographics, pain characteristics and sleep are reported as count and proportions (%) with 95% confidence intervals or means and SDs. For exploration of potential differences between patients with and without OSA, t-tests or Chi^2 tests were used. Possible differences between patients with mild OSA and moderate to severe OSA vs no OSA were explored using one-way analysis of variance (ANOVA). In addition, because of the different gender ratios between groups and the significant differences between men and women in clinical pain parameters, all parameters were gender adjusted by z-transformation by subtraction of the mean values divided by the SD for men and women, respectively.

To explore performance characteristics of the Berlin questionnaire and the STOP-BANG questionnaire, contingency tables were made using objective RP (verified by PSG) as reference standard. Data were derived from the tables to calculate sensitivity, specificity, positive and negative likelihood ratios, and positive and negative post-test probabilities. The sensitivity measure is the proportion of patients correctly identified with OSA by the questionnaire (compared

to reference). The specificity measure is the proportion of patients correctly identified as not having OSA by the questionnaire. The positive and negative post-test probability measures are the probabilities of the presence of OSA after scoring above or below cut-off on the respective questionnaires. The positive predictive value reflects the probability that a patient is classified with OSA by the questionnaire and the objective assessment. Conversely, the negative predictive value is the probability that a patient is considered no-OSA by the questionnaire and the objective assessment.

Cohen's kappa coefficient was used to explore agreement between objective and subjective (Berlin Questionnaire and the STOP-BANG) classification of OSA. Kappa values of 0.81-1.0 was interpreted as almost perfect agreement, 0.61-0.80 as substantial agreement, 0.41-0.60 as moderate agreement, 0.21-0.40 as fair agreement, and 0.0-0.20 as poor agreement [51].

3. Results

In total, 91 patients were enrolled in the study, but due to complications with sleep while using the provided equipment, one patient withdrew. Therefore, 90 patients (71 women and 19 men; mean age: 47.1±11.0 years) were enrolled in this exploratory study. Based on the clinical examination, patients were classified into the following pain conditions: widespread pain (58%), radiating back pain (13%), neuropathic pain (4%), and regional pain (25%). The average pain duration was 12.3 years (range: 10 months to 44 years).

3.1 Frequency of sleep disordered breathing

Forty-six of the 90 patients were diagnosed with OSA on RP and verified by PSG (prevalence of 51.1% [95% CI 40.3% - 61.8%]). Twenty-eight patients had moderate to severe OSA (prevalence of 31.1% [95% CI 21.8% - 41.7%]), and 18 patients had mild OSA (prevalence of 20% [95% CI 11.7% - 28.3%]).

3.2 Self-reported socio-demographics, pain and sleep characteristics in patients with and without OSA

As illustrated in Table 1, patients in the OSA group were more often men, had higher age and BMI and neck circumference compared with patients in the no-OSA group. These differences were mainly explained by differences between patients with moderate to severe OSA compared with patients with no OSA. In addition, the score on the KSQ sleep quality subscale was lower in the OSA group compared with the no-OSA group. This between-group difference was mainly due to differences in the proportions of patients with frequent repeated awakenings and early awakenings. No significant differences were observed for clinical pain characteristics, insomnia, or sleepiness. As illustrated in Table 2, similar findings were observed for the gender-adjusted values.

3.3 Performance characteristics for the two OSA screening questionnaires

In total, 56 patients (62.2%) were classified with high risk of OSA based on the Berlin Questionnaire. The contingency table is presented in Table 3 and performance characteristics are shown in Table 4. The Berlin questionnaire showed a sensitivity of 78.6% (correctly identified by the questionnaire as OSA) and a specificity of 45.2% (correctly identified by the questionnaire as not having OSA). The negative predictive value was 82% (i.e. the probability that a patient with a negative questionnaire is also classified as no-OSA by the objective assessment). The positive

predictive value was 39% (i.e. the probability that a patient with a positive questionnaire is also classified with OSA based by the objective assessment). Examination of the agreement in classification of OSA based on the questionnaire versus objective assessment showed a significant but poor agreement ($\kappa = 0.18$ (95% CI: 0.03 to 0.35), $P = 0.03$).

In total, 46 patients (51.1%) were classified with high risk of OSA based on the STOP-BANG questionnaire. The contingency table is presented in Table 3 and performance characteristics are shown in Table 4. The STOP-BANG questionnaire showed a sensitivity of 71.4% (correctly identified by the questionnaire as OSA) and a specificity of 58.1%. The negative predictive value was 82%. The positive predictive value was 44%. Examination of the agreement in classification of OSA based on the questionnaire versus objective assessment showed a significant and fair agreement ($\kappa = 0.25$ (95% CI: 0.07 to 0.18), $P = 0.01$).

Discussion

This study demonstrated a high frequency of 51.1% of patients with OSA, with 31.1% presenting the moderate-to-severe manifestation. Furthermore, gender-adjusted estimates of pain characteristics, reports of insomnia, and sleepiness did not differ between OSA and no-OSA groups. Performance characteristics of the Berlin questionnaire showed a sensitivity of 76.8% and specificity of 45.2%, with a significant but poor agreement with objective RP assessments. The STOP-BANG questionnaire had a sensitivity of 71.4% and specificity of 58.1%, with a significant fair agreement with RP assessments. Both questionnaires had acceptable negative predictive values but low positive predictive values indicating a potential clinical utility of identifying patients with low risk of OSA in this sample.

Prevalence of OSA in patients with high-impact chronic pain referred for interdisciplinary treatment

In the current study, 51.1% of patients with high-impact chronic pain were diagnosed with clinical OSA. This finding is in agreement with a recent study on predictive factors for OSA in patients with chronic pain, where 58.8% of patients presented with OSA [52], and a recent meta-analysis on 37 studies which estimated a pooled prevalence of 44% (32% for OSA) for clinically diagnosed sleep disorders in a broad population of patients with chronic pain [13]. Furthermore, the prevalence of moderate-severe OSA is similar to a recent study investigating sleep characteristics in chronic musculoskeletal pain patients (31.1% and 28.6%, respectively) [53]. The prevalence of OSA in the current cohort is much greater than what has been estimated in the general population. For instance, the well-known Wisconsin Sleep Cohort Study estimated the prevalence of SDB to be 6.5% in women, and 17% in men, whereas a more recent population-based study investigated 2,121 people and reported a prevalence of 23.4% in women and 49.7% in men [54,55]. As such, even if the estimated prevalence of SDB in the general population may increase due to advancements in technology and guidelines [37] for the diagnosis of e.g. OSA [56], it is important to recognize the high prevalence in chronic pain populations. In a large-scale retrospective study, an OSA prevalence of 13.8% out of 4,036 chronic spinal pain patients was reported [57]. Furthermore, sleep disturbances are commonly reported in patients with fibromyalgia [18] and osteoarthritis [58,59]. The current study supports and extends these findings by showing a similar high prevalence of diagnosed OSA in patients with high-impact chronic pain referred for interdisciplinary treatment. As it is known that OSA incidence increase with age (in particular between ages 40-60) [60], it should be considered if the higher prevalence reported here, is due to age differences between the included participants and earlier study cohorts. When compared to the

Wisconsin Sleep Cohort study, the included cohort is younger (48.4 ± 7.7 years versus 47.1 ± 11, respectively) [55], and similarly younger when compared to a recent large-scale OSA study in the general population [61]. Age alone, can therefore not explain the higher prevalence in OSA in our sample of high-impact chronic pain patients. It is also worth noting that half of the current sample was on prescription opioids for pain management, however no difference in opioid use between mild and moderate-to-severe OSA was found. However, it is important to note that the current study was not powered to investigate differences in opioid use in mild versus moderate-to-severe OSA. Similar percentages of opioid use were reported in a recent large-scale study in more than 12,000 patients with high-impact chronic pain in Denmark [40] which found that 39.1% of women and 51% men were using opioids at the time of attendance. Opioid-induced SDB has been extensively studied [62–64], and a recent systematic review and meta-analysis reported a SDB prevalence of 63% and 91% in non-cancer chronic pain patients on prescription opioids, attending pain or sleep clinics, respectively [65].

4.2 Clinical characteristics in patients with and without OSA

Findings from the current study did not suggest a difference in pain intensity, insomnia complaints or sleepiness when comparing patients with and without OSA, although scores on average pain intensity approached significance suggesting higher pain intensity in patients with moderate to severe OSA. A recent systematic review found substantial differences in pain outcomes (increased pain intensity or decreased pain tolerance) when comparing patients with and without OSA [66]. Co-occurrence of OSA and insomnia is well-established [67], and an explanation for the discrepant findings may be, that since insomnia complaints were not different between the groups, sleep disturbances were not of sufficient magnitude to affect general pain perception as seen in e.g. knee

osteoarthritis patients with and without insomnia [68]. It could be speculated that co-morbid insomnia may be one mediating factor for increased pain perception in high-impact chronic pain patients, independent of clinical OSA or not, but is outside the scope of the current report.

Conversely, KSQ sleep quality was significantly worse for the OSA group when compared to the no-OSA group. While patients with high-impact chronic pain have increased mortality rates when compared to the general population [69], it is still unclear if and how the high prevalence of OSA may affect this. However, OSA is associated with increased risk of cardiovascular diseases, e.g. through intermittent hypoxemia, vascular endothelial dysfunction, and oxidative stress [70], and is known to increase all-cause mortality [71]. This emphasizes the importance of early identification of OSA in patients with chronic pain, since a recent state-of-the-art article outlined that the use of continuous positive airway pressure effectively improved quality of life, mood, and work productivity, and lowers risk of cardiovascular events [72]. As such, future studies are encouraged to investigate the prevalence of OSA in patients with chronic pain and its association with mortality and e.g. comorbid cardiovascular diseases.

In the current study, there was a lower proportion of patients in the no-OSA group reporting frequent repeated and early awakenings on the KSQ as compared to the OSA groups, with a possible dose-response pattern with more repeated and early awakenings, the worse the sleep problems become. This, however, remains a speculation for now, given the sample sizes and potential power issues. Daytime sleepiness, as reflected by the ESS, and insomnia, as measured by the ISI, did not differ between the no-OSA and OSA groups, which is surprising since these are two of the main symptom clusters related to OSA. Possible explanations are that the OSA measure (current AHI-scoring) is too sensitive thereby identifying less symptomatic patients or that there are characteristics related to having chronic pain that may mask OSA-symptoms. In contrast, an

earlier large-scale study suggested an association between daytime sleepiness and SDB in men, but not in women [73], yet contrasting findings are available in e.g. atrial fibrillation patients [74] and general population [61]. As such, the utility of including the Epworth Sleepiness Scale in assessing potential OSA, remains questionable, which is further supported by the current study. For insomnia, Cho et al. [75] showed that in 476 patients with OSA, 29.2% of the patients also presented with insomnia, which is further supported by a recent systematic review and meta-analysis which estimated a 27-29% prevalence of insomnia in patients with OSA [76]. The current results suggest that while insomnia is reported in patients with chronic pain, this may not be related to the presence of co-morbid OSA. Future studies could focus on investigating the relationship between the clinical presentation of e.g. mild versus moderate to severe OSA and awakenings, and possibly how this may relate to pain as earlier evidence suggest that co-morbid OSA or insomnia may impact pain intensity reports in patients with chronic pain [77].

4.3 Classification of patients with high risk of OSA based on the Berlin and STOP-BANG questionnaire and performance characteristics

The Berlin questionnaire identified 62.2% of the cohort to be at high-risk for moderate-to-severe OSA. Similar findings were reported in a study on 316 patients recruited from respiratory clinics, where 69.7% and 77.5% where identified at high risk for OSA, depending on allocation into a home-based sleep test or hospital-based PSG group [78]. The sensitivity and specificity were found to be 78% and 23% when predicting an apnea-hypopnea index ≥ 15 as diagnosed by PSG [78]. The current study agrees with respect to the sensitivity, but with a higher specificity which may be due to the difference in patient populations included (patients with high-impact chronic pain versus patients referred for suspected OSA). Moreover, a systematic review and meta-analysis on the

performance characteristics of the Berlin questionnaire estimated a sensitivity and specificity of 69% and 83%, respectively in general populations and 69% and 56%, respectively in surgical populations, when using PSG as reference [79]. As such, the current findings support that the Berlin may have modest-to-high sensitivity for detecting OSA. However, as the Berlin questionnaire had an acceptable negative predictive value but a low positive predictive value it seems most useful for identifying patients with low OSA-risk in the current sample.

The STOP-BANG questionnaire identified 51.1% of the included patients to be at high-risk for OSA. In agreement, an earlier study found, that in 305 chronic pain patients, 58.2% of the patients screened positive for OSA by the STOP-BANG questionnaire [80]. Unfortunately, the previous study did not report on polysomnographic diagnosed OSA to confirm the validity of these findings. Another recent study conducted in 204 patients with chronic pain, found that for each one-unit increase in the STOP-BANG score, odds for moderate-to-severe OSA was increased by 70% [52]. The STOP-BANG questionnaire sensitivity and specificity for OSA in the current study showed lower sensitivity and specificity when compared with earlier evidence (sensitivity and specificity for OSA: 92.9% and 43%) [31]. The discrepancy may be due to differences in the included populations, as the current study employed the STOP-BANG questionnaire in patients with high-impact chronic pain. In addition, the current results indicate that patients with OSA were older, had higher BMI, and larger neck circumference as compared with patients without OSA. Further, when compared to a recent large-scale publication in high-impact chronic pain [40], the included cohort had slightly higher BMI, which may have affected the performance of the STOP-BANG questionnaire. This is in line with the original STOP-BANG questionnaire validation study which also reported that BMI > 35 kg/m^2, age > 50 years, and neck circumference > 40 cm greatly increased the positive predictive value for OSA [31]. Like the Berlin questionnaire, the STOP-

BANG questionnaire had an acceptable negative predictive value but a low positive predictive value, and implementation of the STOP-BANG questionnaire may aid in identifying persons with low OSA risk in high-impact chronic pain patients.

4.4. Clinical implications

The STOP-BANG and Berlin questionnaire can be used to identify patients with low risk of OSA. Among those with a higher risk, and based on the current findings, it can be recommended that clinicians systematically ask high-impact chronic pain patients about their sleep patterns. This should also encompass plausible comorbidities such as insomnia, cardiovascular diseases, diabetes, as well as willingness to comply with the treatment (continuous positive airway pressure) for OSA, which has notoriously suboptimal compliance rates (reported 68-84%) [81].

4.5 Limitations

The current exploratory study has several limitations. Only 90 patients were included. This, however, is unlikely to have affected the reported sleep disturbances, as a recent large-scale study (n=12257) in high-impact chronic pain [40] demonstrated similar percentage reports of difficulties falling asleep (64.3% versus 67.6%, current findings versus large-scale study, respectively), disturbed/poor sleep (81% versus 80.5%), repeated awakenings (61% versus 70.2%), and early awakenings (57.1% versus 62%). One limitation is that data on the inclusion and retention rate are not available, and we can therefore not exclude that a predominance of patients with greater sleep disturbances are represented in the current study. However, we find that unlikely as the percentages reporting sleep problems (as reported above) are similar to findings in other larger-scale studies. Furthermore, as no a priori sample size calculation was performed, the current study may be

underpowered, particularly for the three group comparisons (no OSA versus mild versus moderate-to-severe OSA). It is suggested that findings between the three subgroups are interpreted with care. Another limitation is that PSG was solely performed when RP showed an AHI > 5. RP is normally known to underestimate OSA since it does not take into account the actual sleep duration (total sleep time) and applies less sensitive scoring of hypopneas (based only on desaturations, not cortical arousals) [82]. We can therefore not rule out with certainty that OSA was present also in patients that did not undergo PSG. However, RP is an accepted modality for diagnosing OSA by ICSD-3 [35].

4.5 Conclusions

The current exploratory study demonstrates a high prevalence of OSA in patients with high-impact chronic pain referred for interdisciplinary pain treatment; however, the clinical pain profile was not worse in patients with OSA. While the percentage identified with high risk of OSA in this sample by the Berlin and STOP-BANG questionnaires was similar to earlier reports, the current findings report poor performance for both questionnaires, when evaluating the agreement with gold-standard diagnosis of OSA, questioning their clinical utility in identifying OSA in patients with high-impact chronic pain. Future studies are encouraged to investigate the benefit of including early screening questionnaires for OSA and whether interventional strategies to combat e.g. moderate-to-severe OSA may improve clinical outcomes in this sample.

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Informed Consent: Written informed consent was obtained from all patients included in this study.

Ethical Approval: This study was approved by the local ethics committee (S-20160129) and The Danish Data Protection Agency.

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