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Polysomnographic characteristics in nonmalignant chronic pain populations: a review of controlled studies

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Summary

Sleep and pain are critical homeostatic systems that interact in a bidirectional manner. Complaints of sleep disturbance are ubiquitous among patients with chronic pain disorders, and conversely, patients with persistent insomnia symptoms commonly report suffering from chronic pain. Sleep deprivation paradigms demonstrate that partial or complete sleep loss induce hyperalgesia, possibly due to shared mechanistic pathways including neuroanatomic and molecular substrates. Further, chronic pain conditions and sleep disturbances are intertwined through comorbidities, which together cause detrimental psychological and physical consequences. This critical review examines 29 polysomnography studies to evaluate whether nonmalignant chronic pain patients, as compared to controls, show differences in objective measures of sleep continuity and sleep architecture. Whereas these controlled studies did not reveal a consistent pattern of objective sleep disturbances, alterations of sleep continuity were commonly reported. Alterations of sleep architecture such as increases in light sleep or decreases in slow-wave sleep were less commonly reported and findings were mixed and also inconsistent. Methodological flaws were identified, which complicated interpretation and limited conclusions; hence, recommendations for future research are suggested. Knowledge of abnormalities in the sleep process has implications for understanding the pathophysiology of chronic pain conditions, which might also direct the development of novel intervention strategies.

Keywords

sleep; nonmalignant; chronic pain; insomnia; sleep deprivation; sleep disturbance; sleep continuity; sleep architecture; polysomnography; review

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Introduction

Sleep and perception of pain both play important roles in the health and survival of a human being. A growing body of evidence, derived from experimental and prospective longitudinal studies, implies a bidirectional relationship between these essential homeostatic systems, with a stronger causal influence of sleep on pain, than pain on sleep [1,2]. Mechanistically, regulation of wake, sleep and nociception share common neuroanatomic and molecular substrates, but the contribution of possible neurotransmitters, endogenous opioid systems and inflammatory cytokines, in the regulation of the interaction between sleep and pain remains largely unknown [1,3]. Research in this area is challenging due to the heterogeneity in the mechanisms that contribute to different chronic pain conditions, as well as the expression of sleep problems in relation to chronic pain. Understanding this relationship is a first step in the development of treatments that target either sleep or pain, which might have salutary effects on either sleep or pain perception.

About 50% of people with persistent insomnia disorder report suffering from chronic pain, and conversely, the same percentage of people with chronic pain meet criteria for persistent insomnia disorder [4]. Complaints of sleep disturbance are ubiquitous among patients with chronic pain disorders (67-88%) [1], and have been correlated not only with increased pain, but also to daytime dysfunction, mood disturbance, impaired cognition and fatigue [5-7]. The connection between chronic pain conditions and sleep disturbances is further strengthened through several shared comorbidities, which possibly create vicious cycles to contribute to a multitude of detrimental psychopathological and physical consequences [4,8]. For example, cardiovascular disease, neurologic disease, affective disorders, cognitive impairment, decreased quality of life, and elevated all-cause mortality are all associated with chronic sleep complaints and insomnia [4,9,10]. Besides the direct impact of pain and its comorbidities on sleep, some widely used pain medications, such as opioids, may exert direct negative effects on sleep profiles [11-13]. In the United States, the combined direct and indirect societal costs for chronic pain and insomnia are staggering, possibly exceeding \$700 billion annually [14,15].

Reviews of studies utilizing various sleep deprivation paradigms have clearly demonstrated that disturbance of sleep continuity induces increased pain perception and hyperalgesic effects [1,16]. Research aiming to elucidate the pathophysiological mechanisms underlying these effects is emerging, and has implicated decreased activity in descending inhibitory monoaminergic or opioidergic pathways that inhibit nociception at the spinal level [17,18]. However, the variability in pain response is complex and influenced by other factors, such as, for example, alterations in cognitive function associated with concomitant fatigue and mood disturbances, with other mechanisms also implicated. [1,16]. Furthermore, sleep complaints and patterns of sleep disturbances in chronic pain populations are diverse and multifaceted - the type of sleep disruption most detrimental to development and maintenance of pain is currently not known, and experimental sleep deprivation studies do not provide a definite answer to this question as such strategies have routinely targeted only sleep duration [16].

Although there is yet no unequivocal explanation to why we sleep, it is clear that sleep is of crucial importance for restorative processes and energy metabolism, neural plasticity, and the immune system [19-21]. Good sleep is thus thought to be a prerequisite for both physical and mental health. Regulation of sleep homeostasis is incompletely understood, and current hypotheses implicate a myriad of molecules, including cytokines (particularly tumor necrosis factor (TNF) α , interleukin (IL) 1β , serotonin, adenosine, nitric oxide and brain-derived neurotrophic factor (BDNF)) [19,20,22,23]. Inflammatory cytokines are pivotal mediators involved in CNS neuroimmune activation pathways. Given their role in both creation and maintenance of pain in various chronic pain models, as well as regulation of sleep, this review will discuss the relationships between sleep and inflammatory cytokines, although it is beyond the scope of this review to systematically evaluate the role of inflammatory cytokines. [22,24].

Polysomnography (PSG), comprising electroencephalography (EEG), electromyography and electrooculography (additionally often respiration, heart rate and body temperature) is the gold standard method for the assessment of measuring sleep, and sleep disturbances. Specifically, both macro- (sleep continuity, sleep architecture) and microstructure (EEG power spectral analysis) of sleep can be analyzed, which is a great advantage compared to actigraphy data, for example, that provides only an estimate of sleep amounts [25]. Despite its utility in the assessment of sleep, controlled PSG studies in chronic pain populations have to date been relatively limited, in contrast to the high prevalence of sleep complaints in this population. Nevertheless, despite the complexity and high cost of such PSG investigations, several studies have been conducted, but no prior review has systematically evaluated this research to clarify the generalizability and significance of objective sleep disturbances in patients suffering from chronic pain, taking into account methodological quality. This review will extract and analyze PSG data on sleep continuity, sleep architecture, and, when available, EEG power spectral analysis, across adult human chronic pain populations, and identify confounding and limiting factors. The sleep EEG constitutes an electrophysiological correlate to the processes of brain metabolism; thus, knowledge of abnormalities in the sleep process might improve understanding of the pathophysiology of chronic pain conditions. Implications for future research and treatment of chronic pain and sleep disturbances will be outlined.

Basic architecture and physiology of sleep

The dynamic, cyclic process of sleep is divided into non-rapid-eye-movement (NREM) sleep, traditionally stages 1-4 with the deepest stages 3-4 referred to as slow-wave-sleep (SWS) or N3, and rapid-eye-movement (REM) sleep (Table 1) [26]. SWS predominates during the first third of the night, whereas REM sleep predominates during the last half of the night. Each NREM to REM sleep cycle lasts about 80-110 minutes, and over the course of the night these cycles are repeated three to six times. The conventional staging of sleep is done through visual inspection of the EEG. To achieve a quantitative analysis, a mathematical approach called EEG power spectral analysis is utilized [27]. Spectral analysis describes the frequency content of an EEG signal, which provides a continuous and exact evaluation of the power spectrum density. This method enables detection of trends in EEG

power density throughout the night, and also detection of faster frequencies superimposed on slow-waves.

Search methods

A review of the literature was conducted, using the PubMed search engine, Google Scholar, and a manual search of all identified pertinent references. The database searches were performed in October-November 2014, covered the time period from January 1990 to November 2014, and employed the following search terms individually and in combination: chronic pain, sleep, polysomnography, objective, electroencephalographic, fibromyalgia (FM), rheumatoid arthritis (RA), osteoarthritis (OA), migraine and other specific chronic pain conditions (Figure 1). The language of publications was not an explicit exclusion criterion. For inclusion, the original studies utilizing PSG in chronic pain populations fulfilled following predetermined criteria: performed on adults; have at least one pain-free control group (i.e., controlled study); and not contain an experimental study protocol (i.e., no sleep deprivation paradigm). Ambulatory PSG studies were considered for inclusion. Focus was directed towards extracting information on all sleep macrostructure variables (total sleep time (TST, min), sleep onset latency (SOL, min) = time to accomplish transition from wakefulness to sleep (any NREM stage), wakefulness after sleep onset (WASO, min), sleep efficiency (SE) = (TST/time in bed (TIB)) x 100, number of awakenings, number of sleep cycles, number of sleep stage shifts/hour, duration of NREM sleep stage 1 (N1), NREM stage 2 (N2), NREM stage 3 (N3), REM sleep duration, REM latency, REM density, arousal index (ArI) = number of arousals/hour), microstructure variables (EEG power spectral analysis parameters), apnea/hypopnea index (AHI, number of abnormal breathing events (apnea = cessation of airflow ≥ 10 s; hypopnea = at least 50% reduction of the airflow ≥ 10 s)/hour), and periodic limb movements during sleep (PLMS) index = number of PLMS/hour). Given the comprehensive range of sleep parameters of interest, actigraphy data were deemed insufficient to contribute to the synthesis of the review; hence, actigraphy studies were excluded.

Controlled PSG studies in chronic pain populations

The vast majority of all controlled PSG studies in chronic pain populations have included patients suffering from FM or chronic widespread pain (CWP), but during recent years additional chronic pain entities have been examined. Brief summaries of results from all identified studies (Table 2), fulfilling the inclusion criteria described above, will be provided in this section, and an overview of the most important objective findings are outlined in Table 3. Confounding factors, such as medications, composition of control groups, pain duration, gender and age, are outlined in Table 2, and for clarity, comments and analyses regarding these and other factors will be provided in a coherent way in the corresponding section below.

Fibromyalgia and chronic widespread pain

Among the 19 studies that evaluated PSG in fibromyalgia (FM) and chronic widespread pain (CWP) patients, the vast majority utilized the diagnostic criteria of 1990 American College of Rheumatology for FM. Hence, despite revision of diagnostic criteria in 2010 [28], FM

patients included in these studies fulfilled the following criteria: chronic widespread pain; at least 11 of 18 tender points rated as painful.

FM is a prevalent condition with 2-8% of the population fulfilling diagnostic criteria [29]. In addition to reports of chronic bodily pain, the vast majority of FM patients also report increases in feelings of fatigue, along with unrefreshing sleep, daytime dysfunction and insomnia symptoms. Indeed, virtually all FM patients (96-99%) experience some form of sleep difficulties [30-32]. In turn, poor sleep quality among FM patients is a strong predictor of both fatigue, and pain [1,2,31-33], and conversely pain negatively influences sleep as demonstrated in some longitudinal studies [1,2].

Subjective sleep findings: a context for polysomnography results in FM and CWP

Despite the focus of this review on PSG results, the relatively larger number of PSG studies (n=19) conducted in FM and chronic widespread pain (CWP) populations offers an opportunity to summarize subjective sleep findings as a context to understand the PSG results. Importantly, in this brief summary based on all 19 PSG studies, we found that study methodologies differed substantially across studies, in terms of subjective measures, which ranged from single items to use of validated questionnaires and structured interviews; hence, confounding factors and methodological issues are systematically addressed. Furthermore, a majority of the FM studies published in the 1990's reported results on very small numbers of subjects (<15).

With the exception of the *Horne and Shackell* study [34], which included only subjective good-sleepers, subjective ratings of insomnia symptoms, sleepiness and fatigue were significantly higher among FM and CWP patients than HC. Almost all patients reported complaints of poor sleep [35-48], although five of the studies provided no subjective sleep measures [49-53]. Interestingly, despite FM subjects' frequent complaints of easy awakening from sleep along with daytime sleepiness, *Chervin et al.* [46] and *Roehrs et al.* [47] were not able to corroborate these findings through objective testing (auditory arousal thresholds and multiple sleep latency tests, MSLT). Moreover, FM subjects reporting daytime hypersomnolence exhibited more tender points, higher ArI and lower SE, than those lacking this symptom [41]. Interestingly, one study showed that a specific pattern of phasic alpha activity was correlated with longer pain duration, low sleep quality scores and both subjective and objective increases in morning pain [42]. Symptoms of pain also appear to be related to sleep problems in the FM population. For example, FM subjects exhibited significantly higher pain scores, and more pain at awakening, compared to HC [36-39]. Whereas psychopathology and psychological distress are reported to be highly prevalent among FM patients [34-36,39,43,44], some studies did not specify whether co-morbid mood disorders might have confounded the results [48,51,53]. Nevertheless in other studies, structured clinical interviews were implemented to exclude subjects with any concurrent psychiatric illness [45,46]. Finally, in two studies [36,39], cognitive disturbances were measured and detected, but although FM patients reported lower accuracy on complex performance tasks, it was only objectively shown that they had lower speed, but not accuracy, on these tasks.

Polysomnographic macro- and microstructure sleep findings in FM and CWP

No consistent alterations of sleep macro- or microstructure were found in FM or CWP, although disturbances of these objective measures of sleep were identified in several studies. Among those studies that examined sleep continuity, the following changes were found in FM or CWP patients as compared to HC: decreased TST [41,43,47,48,51-53], increased SOL [34,38,44,48,53], decreased SE [41,43,44,48,49,52,53], increased WASO [47,49,51], and increased number of awakenings [36,37,48,51]. Interestingly, and partially as a result of the methodological heterogeneity, the numerical values of sleep continuity measures varied quite substantially between studies, with TST ranging from 288±71 [53] to 475±59 [40] min, SOL 12±5 [45] to 33±15 [52] min, SE 75±14 [53] to 93±10 [34] %, and WASO 19±10 [51] to 64±44 [53] min. Sleep continuity measures were not reported in two publications [37,42], and WASO comparisons were not provided in 11 publications [34-36,38-41,43,48,50,52].

In contrast to the sleep continuity finding, no uniform changes of sleep architecture were found. In 10 studies, various significant sleep architectural alterations were identified: increased N1 [39,41-44,49], decreased N1 [35,50], decreased N2 [37,44], increased N2 [51], decreased N3 [41,43], isolated decreases of N3 stage 4 [37,51], decreased REM [35,37], decreased number of sleep cycles [48,52], and increased number of sleep stage shifts [45]. However, one consistent finding is that no study reported any changes in REM latency; REM density was not provided in any of the publications. ArI was only reported in a few of the publications, and was found to be either elevated [36,41,43], or unchanged [42,53], as compared to HC.

Although most studies obtained AHI and PLMS index, three publications did not report these indices [34,38,49], and it was only clearly specified in four of the publications that the indices were used to exclude patients with primary sleep disorders [35,39,45,47]. However, PLMS index was only found to be increased in two studies [51,52], and, when measured, there were no significant differences as to AHI between the groups.

Visual identification of alpha-delta intrusion, i.e., spontaneous occurrence of alpha-waves in delta sleep, also showed equivocal results [35,37-43,50,51]. EEG power spectral analysis was implemented in seven of the studies [34,37,38,42,46,48,49] and alpha frequency band analysis revealed various findings, such as increased power in N3 [38], increased power in N2 and N3 during the first two sleep cycles [42], or throughout all sleep cycles [49], increased alpha-delta ratio [37], or no significant differences [34,46,48]. Although constituting a small (n=7), controlled PSG study in FM, the early work by *Molony et al.* did not report enough variables to be included [54].

Rheumatoid arthritis

In contrast to FM, which is thought of as a centralized pain state [29], most manifestations of rheumatoid arthritis (RA) are viewed as secondary to peripheral nervous system and immune system dysfunction, and the pain is typically localized to the joints and surrounding tissues. RA is a systemic inflammatory, autoimmune disorder, which, if left untreated, destroys synovial joint tissue, and thus disrupts joint structure and function [55]. In addition

to symptoms including joint pain and joint swelling, as well as morning stiffness (previously [56], but no more a diagnostic criterion [57]), complaints of fatigue and disturbed sleep are highly prevalent in RA patients. Clinically significant sleep disturbance, as measured by Pittsburgh sleep quality index (PSQI) score > 5, is found in over 60% of RA patients [58], and mean scores range from 5.9 to 7.8 [58-60]. Sleep disturbance in RA is primarily determined by pain, mood disturbance (e.g., depression), and disease activity [5,59-61], factors that are also linked to daytime fatigue [6].

To date, three controlled PSG studies have been performed in RA patients. *Hirsch et al.* [62] found evidence of sleep fragmentation among RA subjects, demonstrated by significantly increased SOL, WASO, number of awakenings, and significantly decreased SE, but there were no differences regarding sleep architectural parameters between the groups. Of this sample, 11 of the 19 RA patients had active disease, and a high number exhibited PLMS (14/19). Interestingly, most RA patients felt rested and perceived themselves as having enough sleep; only one subject showed evidence of objective abnormal daytime sleepiness, as measured by MSLT. Whereas *Hirsch et al.* examined a mixed group of in- and outpatients, *Drewes et al.* [63] focused on outpatients. Nevertheless, as compared to the sample in *Hirsch et al.*, the sample studied by *Drewes et al.* reported a higher number of swollen joints (9.6 ± 9.0 vs 7.9 ± 4.2), and higher Ritchie articular index (14.4 ± 12.3 vs 10.1 ± 5.7), although patients reported a shorter duration of morning stiffness (64.5 ± 77.3 vs 87.4 ± 86.9 min) and had lower erythrocyte sedimentation rate (22.3 ± 14.3 vs 37.2 ± 26.6 mm/h). As compared to HC, RA patients showed elevated PLMS index (10.8 ± 16.3 vs 4.1 ± 9.0 movements/h), although no macrostructure sleep parameters were found to differ between the RA patients and HC. Furthermore, comparison of PSG variables between an RA subgroup with more active vs less active disease did not demonstrate any differences. Spectral analysis showed increased power in the alpha frequency band during N2 and N3, and there were no differences as to the expected decline in total amount of delta power during sleep cycles. Nevertheless, despite the absence of differences in the objective measures of sleep, RA patients had more difficulty initiating sleep, poorer sleep quality, and higher daytime sleepiness compared to HC. Finally, in the study by *Roehrs et al.* [47], 75% of RA patients reported subjective sleeping difficulties, which was similar to the frequency of sleep complaints for FM patients who were also being examined. RA patients had significantly lower TST and higher WASO compared to HC, but no other significant differences were found. In contrast to results for the FM group, the MSLT did not reveal any significant findings for the RA group. *Crosby et al.* also conducted a controlled PSG study in the RA patient population, but several important methodological details were omitted, and only three sleep parameters were reported [64]. It deserves to be mentioned though, that *Crosby et al.* found an increased number of awakenings and decreased TST for RA patients in flare vs HC, and decreased SE for both RA patients in flare and non-flare vs HC.

In summary, disturbance of sleep continuity measures were found in two of the studies (decreased TST [47] and SE [62], increased SOL [62] and WASO [47,62]), although these findings were not confirmed in the one study with the largest sample [63]. No specific sleep architectural alterations were found, but spectral analysis, implemented in one of the studies, revealed increased power in the alpha frequency band during N2 and N3 [63]. Sleep

disorders were excluded from the study by *Roehrs et al.*, but, interestingly, in the two other studies PLMS index was found to be significantly elevated among RA patients [62,63]. Due to the somewhat different subpopulations of RA patients enrolled, some sleep parameter values differed considerably, e.g., SE 81 ± 11 [62] to 94 ± 7 [63] %, WASO 29 ± 36 [63] to 87 ± 47 [62] min, N2 47 ± 10 [63] to 62 ± 2 [47] %, and N3 10 ± 1 [47] to 21 (standard deviation not reported) [63] %, while others were within a close range, such as TST, N1 % and REM %.

Ankylosing spondylitis

Ankylosing spondylitis is the most common and severe spondyloarthritis subtype, with a prevalence rate around 0.2-1.2% [65]. It is a chronic, inflammatory disorder primarily characterized by disease localized to the spine and sacroiliac joints, but sometimes also asymmetrical oligoarthritis and/or enthesitis [65]. Similar to RA, around 50% of ankylosing spondylitis patients have elevated PSQI scores >5 indicating significant sleeping disturbance and mean scores are estimated to range from 6.4 to 6.6 [66,67]. High pain levels, disease activity, and mood disorders are among the most important factors that have been shown to contribute to sleep disturbances in this patient population [66,67].

Only one study was identified that examined sleep using PSG in ankylosing spondylitis patients. *Abdulaziez and Asaad* [68] found a number of significant sleep parameter differences between ankylosing spondylitis patients and HC: increased SOL (32.1 ± 8.0 vs 15.4 ± 2.7 min), decreased SE (75.1 ± 4.3 vs 93.2 ± 2.1 %), increased N1 (4.3 ± 0.8 vs 1.9 ± 0.3 %) and N2 (55.1 ± 1.6 vs 49.6 ± 0.9 %), decreased N3 (18.3 ± 1.0 vs 23.9 ± 0.3 %), and increased ArI (11.9 ± 1.8 vs 4.1 ± 1.7 arousals/h). PLMS index also differed significantly, but levels remained within normal limits in both groups. 90% of the ankylosing spondylitis patients had a PSQI score above five.

Osteoarthritis

OA is among the top 10 causes of disability worldwide, and in older adults in the USA lower extremity OA is the leading cause of mobility impairment [69]. The primary symptom of OA is pain, and sleep disturbances are also common. In a large cohort ($n=613$) of older patients suffering from moderate OA of the hip or knee, the mean PSQI score was 8.0, and 70% had poor sleep [70]. Regression analyses revealed that greater arthritis severity, depressed mood and restless legs syndrome (which was found in 25% of the patients) were independent correlates of poor sleep. Interestingly, treatment of OA with arthroplasty or opioid analgesics, have been shown to improve not only pain, but also subjective and objective measures of sleep [71,72].

Only one controlled PSG study was found that studied an OA population (OA of the hip or knee, or both). In this sample of OA patients, *Leigh et al.* [73] found a significant increase of N1 (23.6 ± 6.9 vs 15.2 ± 3.9 %), and decrease of N2 (47.7 ± 8.2 vs 54.4 ± 7.8 %) as compared to HC. There were no sleep continuity differences between the groups, but it is important to note that both groups had low SE (OA: 81.5 ± 7.9 %; HC: 80.4 ± 7.7 %), and high WASO (OA: 102.8 ± 38.2 min; HC: 85.3 ± 37.0 min), indicating fragmented sleep. All OA patients

were admitted to a hospital for intensive physiotherapy and consideration of knee or hip arthroplasty, which indicates severe OA symptomatology.

Migraine and tension-type headache

Migraine and tension-type headache (TTH) are both thought to be associated with disturbances of sleep. A review of population-based longitudinal and cross-sectional studies showed that these types of headache are significantly related to insomnia symptoms, especially when frequent or severe, and some studies have also demonstrated bidirectional causality [74]. Virtually all sleep disorders, particularly OSA, are more prevalent among headache patients compared to HC, and dysregulation of sleep is a frequent trigger of migraine and TTH [75].

Karthik et al. [76] examined patients suffering from migraine without aura (mean attack frequency 7.4 ± 6.4 attacks/month, mean PSQI score 6.8 ± 3.3), as compared to HC. SE was significantly lower (76.2 ± 13.6 vs 84.7 ± 7.1 %), SOL higher (27.0 ± 23.1 vs 15.1 ± 15.7 min), and stage 4 lower (2.4 ± 3.7 vs 6.2 ± 6.6 %), for migraine subjects compared to HC. Even though stage 4 sleep was lower for the migraine group, N3 did not differ significantly between the groups. Although the number of awakenings was significantly higher for migraine patients, ArI was found to be lower compared to HC. A study by *Engstrom et al.* [77] included migraine patients ($n=53$, 2-6 attacks/month), TTH patients ($n=20$), and HC. Patients with migraine were divided into two groups: sleep migraine (SM) (i.e., headache onsets mainly during sleep and awakening) and non-sleep migraine (NSM) (i.e., daytime headache onsets). Both headache groups had mean PSQI scores exceeding five (migraine 6.6 ± 4.4 , TTH 5.3 ± 3.5). TTH and NSM patients had significantly more N3 than HC (107 ± 21 vs 104 ± 28 vs 86 ± 31 min), but SM subjects had similar amounts of N3 as HC. Besides SM patients having significantly more awakenings than HC, there were no other sleep macrostructure differences between the groups. It is noteworthy that all groups had sleep efficiencies over 90%. Finally, *Kristiansen et al.* [78] conducted a large, cross-sectional, population-based study, but due to the study design, and the fact that participants with high risk of OSA were oversampled, this study could not be included in the review.

Temporomandibular disorders with chronic myofascial pain

Temporomandibular disorders (TMD) constitute a heterogeneous group of craniofacial pain problems involving multiple etiologies [79]. Myofascial pain (MFP) disorder affecting the masticatory muscle system is the most common subtype of TMD, and the pain often extends beyond the jaw, temporomandibular joint (TMJ) and muscles of mastication, to encompass widespread and complex symptomatology. Clinical local manifestations also include limitation or asymmetry of mouth opening, and TMJ sounds, and distinct anatomic pathology is rarely identified in the cases of TMD with chronic MFP [79]. A large survey among TMD patients demonstrated high frequencies of painful comorbidities, such as headaches and FM, but also, e.g., psychopathologies and OSA [80]. These high rates of OSA have not been confirmed through a well-powered PSG-study [81], but clinically significant insomnia is prevalent [82], and insomnia symptom severity is prospectively associated with increased pain in TMD patients [83].

To date, two controlled PSG studies examining patients suffering from TMD with MFP were identified. *Rossetti et al.* did not report any significant sleep macrostructure differences between TMD patients and HC [84], while *Dubrovsky et al.* demonstrated mild sleep fragmentation through significantly increased levels of N1 for TMD patients compared to controls (12.2 ± 7.6 vs 9.2 ± 5.0 %) [81]. There was also a trend towards a higher number of awakenings for the TMD group, and although the total ArI did not differ significantly, TMD patients had a significantly higher respiratory ArI. Interestingly, post-sleep ratings of MFP significantly predicted lower SE and a higher number of awakenings.

Mixed chronic pain populations

Schneider-Helmert et al. [85] compared a heterogeneous group of “non-organic” chronic pain patients complaining of insomnia (11 FM, 10 headache/migraine, 5 low-back pain) to a group of pain-free chronic primary insomniacs. Given that the comparison group suffered from chronic insomnia, there were no significant differences for any of the sleep continuity or sleep architecture parameters between the groups, but the numerical mean values found among chronic pain patients indicate severe sleep disturbance: TST 283 ± 68 min, SOL 54 ± 43 min, SE 58 ± 13 %, and WASO 150 ± 56 min. Compared to normal values, both proportion and minutes of SWS were strikingly reduced for both groups. Interestingly, there were no sleep parameter differences between chronic pain patients reporting pain on the recording night ($n=10$), as compared to those in the group who were temporarily pain-free. Consistent with the objective sleep data findings, subjective sleep measures were similar between the groups, and overall, the degree of sleep disturbance was indistinguishable between the chronic pain patients and primary insomniacs. In an ambulatory PSG study conducted by *Blagestad et al.* [86], a mixed population of older chronic pain patients was compared to HC. The chronic pain patients displayed significantly decreased SE (81.2 ± 9.6 vs 89.5 ± 6.0 %), increased WASO (94.1 ± 52.3 vs 45.0 ± 26.1 min), and an increased number of awakenings (14.3 ± 9.3 vs 9.2 ± 4.6) as compared to HC. Microstructure analysis revealed a reduction of EEG power in the delta frequency range for chronic pain patients compared to HC. A study by *Wittig et al.* [87] found evidence of sleep fragmentation in a group of patients suffering from chronic pain for which no “physical etiology” could be found, but due to its year of publication (1982) it was not included in this review.

Confounding and limiting factors

A number of methodological factors complicate systematic comparison and interpretation, which require consideration.

Adaptation night

Adaptation night was missing in seven of the studies [37,51,52,68,76,77,85]. This potentially introduces the confounding first-night effect, i.e., disturbance of sleep due to the circumstances of sleeping in a sleep laboratory environment, or being hooked-up to EEG equipment. Also, only sleeping two nights in a sleep laboratory might be insufficient to reflect the true variability of sleep in chronic pain patients.

Ambulatory studies

Three of the PSG studies were ambulatory, which may provide results better resembling the natural sleep patterns for these patients [34,49,86], although concerns have been raised about the quality of ambulatory as compared to laboratory based sleep studies.

Matching of control groups

Many variables influence outcomes, but the importance of the matching of control groups must be stressed. While most control groups were matched for age, gender was only matched in ten studies [37,53,62,63,76,77,81,84-86], BMI in seven studies [40-45,53], and menopausal status in merely three studies [40,42,45]. Ethnicity was often omitted from the basic demographics, and only two studies clearly stated that the controls were ethnicity-matched [37,81]. All of these factors, and others such as socioeconomics and physical activity, are potential confounders given their effects on various sleep parameters [88-93]. Also, although other sleep-influencing factors, e.g., cigarette smoking, intake of alcohol, caffeine or other stimulants were typically avoided during the course of the studies, monitoring of use prior to or during the sleep protocol was not reported.

Gender

Given the large female preponderance in these studies, generalizability of the results to males is difficult, especially for FM. It is, however, important to note that several types of chronic pain are more prevalent among women, which also reflects recruitment strategies.

Subjective sleep status

Typically the control group consisted of subjective “good-sleepers”, but this was not the case in all studies, and the subjective sleep status of included pain populations differed, which of course reflects upon objective findings.

Sleep-influencing medications

Although most study protocols implemented a washout period (typically 14 days) for sleep-influencing medications prior to PSG, there were important differences, and information regarding medications was often insufficient to allow systematic comparison. Some pharmacological agents used in the treatment of chronic pain conditions exert negative sleep modulatory effects, e.g., opioids (reduced SWS, dose-dependent REM suppression), and selective serotonin reuptake inhibitors (reduced TST, increased WASO, reduced REM sleep), while others might confer positive effects, such as improved sleep continuity and/or increased SWS (tricyclic antidepressants, gabapentin, and pregabalin) [11-13]. It must also be taken into account that most of these drugs contribute to daytime somnolence, which potentially affects cognitive performance and pain perception. Besides primary and adjuvant analgesics, also other classes of drugs influence sleep, such as beta blockers and should be taken into consideration [94].

Duration of chronic pain

The duration and/or severity of the chronic pain conditions were often omitted. The pathophysiology of persistent pain, including central neuroimmune activation and dysfunctional neuroplastic alterations, is more complex the longer the pain remains uncontrolled, which most likely also affects the associated disturbances of sleep [8,24].

Comorbidities

Although groups of controls were generally not allowed to have any kind of pain condition, painful- and non-painful comorbidities – with potential effect on sleep physiology – were not consistently considered in many studies. This limitation is especially true for mood disorders, such as depression and anxiety, which are closely related to disturbance of sleep [95]. Ideally, structured clinical interviews should be the basis for these diagnoses, but this was only implemented in two studies [44,45]. Also, information regarding primary sleep disorder screening was sometimes lacking or inadequate, and detected abnormalities did not always lead to exclusion.

Primary sleep disorders

Among patients with chronic pain secondary to rheumatologic disorders there is a high prevalence of primary sleep disorders, such as OSA, PLMS and restless legs syndrome (RLS) [7]. In addition, many medications used in chronic pain populations are associated with these sleep disorders [13], but the exact clinical significance of, e.g., moderately increased PLMS index, also found in patients with various other medical disorders, is unknown. The nature of the relationship between chronic pain states and comorbid primary sleep disorders has to date not been fully elucidated. Nocturnal hypoxemia has in a few OSA studies been shown to correlate with self-reported pain and headache, and continuous positive airway pressure treatment was in a small sample of pain-free severe OSA patients found to reduce laboratory pain sensitivity, but conflicting findings exist [96].

Subjective clinical measures

Subjective sleep, pain and mood measures ranged from nonexistent to structured interviews and extensive use of comprehensive validated scales. It is quite remarkable that some of these studies examining chronic pain populations did not even contain a subjective pain assessment (i.e., visual analog scale). Comprehensive qualitative and quantitative measures are necessary to facilitate analyses of correlations between objective and subjective sleep and pain parameters.

Besides these confounding factors, it deserves to be mentioned that, although the definition of SE is undisputed, and most publications specified that SE was a function of TIB, both TIB and/or total recording time were not consistently provided, which introduces a degree of uncertainty regarding calculation of SE. However, when both TIB and total recording time were provided, they were nearly the same, and based on the available data, the conclusion that SE was decreased in a number of the studies still holds. Finally, the 29 included publications span over three decades, which means that diagnostic criteria for some of the

chronic pain conditions have been modified, introducing a degree of patient population heterogeneity. Methods for interpretation of PSG data are today also more sophisticated as compared to the early 1990's. Given this array of methodological flaws and differences, systematic comparison of the included studies is not without complications and the conclusions presented here require cautious interpretation given the many limitations.

Discussion

This critical review of controlled PSG studies has shown that there does not appear to be a consistent pattern of objective sleep disturbances in nonmalignant chronic pain populations. Given the different etiologies and multitude of involved pathophysiological mechanisms for the wide spectrum of chronic pain conditions, this finding is not surprising. Some examined conditions, such as FM, are mainly of central origin, while others are predominantly due to peripheral nervous system involvement, which is likely to be reflected in the observed, or absent, macro- and microstructure abnormalities. Further, several physiological and psychological factors, and pharmacological treatments, associated with chronic pain states influence sleep, which further complicate the picture.

Disruption of sleep continuity was the most common alteration of sleep macrostructure found across all studies, demonstrated through decreased SE [41,43,44,48,49,52,53,62,68,76,85,86], increased SOL [34,38,44,48,53,62,68,76,85], increased WASO [47,49,51,62,76,85,86], and decreased TST [41,43,47,48,51-53,85]. Alterations of sleep architecture were less common, and more inconsistent. An increase of N1 was found in nine of the studies [39,41-44,49,68,73,81], but it was decreased in two studies [35,50]. Results for N2 were equivocal [37,44,51,68,73], while N3, or its former subcomponents stage 3 and 4 sleep, were decreased in seven of the studies [37,41,43,51,68,76,85]. REM sleep was decreased in only three of the studies [35,37,85]. It is important to note that several studies found no significant differences between pain patients and controls in sleep continuity [35,36,39,40,45,50,63,73,81,84] or sleep architectural measures [34,36,38,40,47,53,62,63,84,86].

Although results are not unequivocal, experimental selective deprivation of SWS or REM sleep has in healthy human subjects generally been shown to produce hyperalgesic effects, indicating antinociceptive properties associated with these sleep stages. However, total, and more importantly, partial sleep deprivation (PSD, continuous 4h sleep restriction), and other sleep continuity disruption models, also produce similar effects, which makes it hard to discern the relative influence of the distinct sleep stages on pain processing [1,16]. Sleep continuity disruption, i.e., fragmentation of sleep, was the most common finding in this review, and models depicting this might, together with PSD, best simulate the sleep disturbances found in chronic pain patients. With a few exceptions [18,97], there is to date a paucity of sleep deprivation studies in clinical chronic pain samples. Indeed, given the heterogeneity of chronic pain conditions, experimental research is needed to understand whether sleep disturbance is driving pain symptoms, and what characteristics of sleep loss are contributing to these effects. Although sleep deprivation studies have been conducted in RA and TMD patient populations without significant adverse effects [18,97], it is not known whether findings generalize to other pain populations. Further, it is not known whether the

effects of sleep disturbance on hyperalgesia may be preferentially driven by short sleep duration or by sleep fragmentation; understanding these respective effects would aid in the development of treatments that target one or another aspect of sleep disturbance to improve pain symptoms. Moreover, there is limited understanding of the mechanisms by which sleep disturbance contributes to hyperalgesia, and research that examines the role of opioid- or inflammatory mechanisms, for example, in mediating the effects of sleep loss on pain, and on differences across patient populations, is needed. Nevertheless, given the ethical issues inherent in such experimental studies, caution must be exercised to minimize risks for these patients, who are likely significantly more vulnerable to the effects of experimental sleep deprivation as compared to healthy subjects, and with greater increases in symptoms of pain and depression (for example [97]).

The observed disturbance of sleep continuity strongly suggests alterations in sleep stability, and dysregulation of the homeostatic processes underlying sleep and wakefulness. The increased light sleep, and decreased levels of SWS, found in a number of the studies, might be significant components behind the experience of daytime symptoms, since SWS is considered to be the most restorative sleep stage, important for sleep maintenance and sleep quality, and also memory consolidation and processing [98]. During SWS, there is a shift in autonomic nervous system balance (sympathetic to parasympathetic dominance) and an alteration of endocrine output (increased release of growth hormone (GH) and prolactin), and disruption of this stage may increase the risk of disease [99]. Interestingly, about 50% of FM patients have GH abnormalities, and addition of low-dose GH to standard treatment of severe FM with low levels of insulin-like growth factor 1 has been shown to improve pain scores [100].

Of the reviewed studies, 10/29 studies implemented EEG power spectral analysis; although results were mixed, alpha power was often increased during N2 and/or N3 [37,38,42,49,63]. Visual scoring of alpha intrusion during NREM sleep yielded ambiguous results, which is in agreement with the previous conclusion that this phenomenon is neither specific nor sensitive for FM, or any other chronic pain condition.

Pathophysiologic mechanisms underlying the connection between sleep and pain

Etiologically, the bidirectional relationship between persistent pain and poor sleep is not well understood, but plausible mechanisms that deserve discussion include central neuroimmune activation, disturbed neurotransmitter balance, and neuroendocrine axis aberrations with the recognition that a comprehensive review of these pathways is beyond the scope of this review. Imbalances in central pro- and anti-inflammatory cytokines have been detected across several human chronic pain populations [24], and these cytokines, especially IL-1 β and TNF- α , have also been found to play a role in the physiological regulation of sleep, and sleep homeostasis [20]. Levels of IL-1 β and TNF- α vary with the sleep-wake cycle, and in animal experimental models, administration of IL-1 β and TNF- α increase NREM sleep in a dose- and time-dependent manner. IL-1 β typically causes sleep fragmentation, high doses actually suppress both REM and NREM sleep, and sleep deprivation has been shown to increase IL-1 β mRNA in the brain [22]. In preclinical chronic

pain models, CNS cytokines have been suggested to be pivotal mediators involved in neuroimmune activation pathways and neuroinflammation, driving the transition from acute to chronic pain [24]. Across a variety of chronic pain states of varying etiologies, some cross-sectional studies have revealed evidence of elevated cerebrospinal fluid (CSF) levels of pro-inflammatory cytokines TNF- α , IL-1 β , IL-6, and IL-8. Also, in complex regional pain syndrome (CRPS), decreased levels of anti-inflammatory cytokines IL-4 and IL-10 are reported [24]. Mechanistically, IL-1 β and TNF- α increase the excitability of dorsal horn neurons (central sensitization) and reduce inhibitory synaptic transmission, through actions partially mediated by microglia. TNF- α also stimulates astrocytes to release monocyte chemoattractant protein-1, which is a critical factor in the pathophysiology of neuropathic pain [24]. In addition to alterations in inflammatory cytokines, other studies have found elevated CSF levels of BDNF in inflammatory and neuropathic pain models, and in clinical pain populations (FM, failed back surgery syndrome and chronic daily headache). BDNF contributes to central sensitization through mechanisms including increased glutamatergic neurotransmission (phosphorylation of N-methyl-D-aspartate (NMDA) receptors), and weakened gamma-aminobutyric acid (GABA)/glycine-mediated inhibition of neural firing [24]. Administration of BDNF into the cortex of awake rats has been shown to locally increase SWS during NREM sleep in the subsequent sleep period, whereas administration of an anti-BDNF antibody or an inhibitor of BDNF TrkB receptors decreased SWS [19]. However, sleep deprivation seems to decrease concentrations of BDNF in several parts of the brain, and the exact role of BDNF in the regulation of sleep homeostasis has not yet been deciphered. Another possible mediator linking sleep and pain is serotonin (5-HT), which is involved in descending pain modulation pathways, affective disorders, and regulation of NREM sleep [20]. In a few animal experimental models, REM sleep deprivation has been shown to decrease levels of serotonin in, for example, the frontal cortex and hippocampus [16], and interestingly, lowered concentrations of serotonin, dopamine and norepinephrine metabolites have been found in the CSF of FM patients [101]. Serotonin exerts complex modulatory effects on nociceptive transmission in the spinal dorsal horn, and depending on type and duration of pain, both pro- and antinociceptive effects can be observed. When serotonin binds to postsynaptic 5-HT_{1A}, or presynaptic 5-HT_{1B/D} receptors, pain inhibitory effects are achieved through diminished excitability of spinothalamic neurons, excitatory interneurons, and inhibited neurotransmitter release from primary afferents [102]. Disinhibition of descending inhibitory pain pathways is a major pathophysiological alteration, implicated as a mechanism contributing to central sensitization in a number of chronic pain states. An emerging body of research is also indicating a role for altered dopaminergic signaling in the connection between disturbed sleep and chronic pain, possibly contributing to dysregulation of wakefulness and disrupted sleep continuity [1]. Finally, preclinical studies have shown that sleep deprivation may inhibit synthesis of endogenous opioids, downregulate central opioid receptors, and also reduce the affinity of μ - and δ -opioid receptors, which might reduce the analgesic efficacy of exogenously administered opioids, but further mechanistic research is warranted [1,16]. Two well-designed studies in human healthy volunteers and chronic temporomandibular joint disorder patients have shown that impaired descending pain-inhibitory function associated with disrupted sleep might be a pivotal mechanism linking sleep and pain [17,18]. Thus, it is likely that undisturbed sleep continuity, and/or undisturbed sleep architecture, is of great importance

for the function of the endogenous descending pain modulatory systems, and potentially also for the action of exogenous analgesics. The complex effects of central cytokines, serotonin, and other neurotransmitters (e.g., acetylcholine, glutamate, and adenosine) on sleep regulation are beyond the scope of this review [20,22,103], but it is obvious that therapeutic modalities directed towards modulating these mediators are of high interest.

Future research

Given the circular, and possibly feed forward interactions between chronic pain and disturbed sleep, increasing attention is being directed towards improving pain and sleep concomitantly. A limited, but growing body of evidence supports benefits of non-pharmacological (e.g., cognitive behavioral therapy), pharmacological (e.g., opioids) and surgical treatments of chronic pain conditions on sleep and pain outcomes simultaneously [71,72,104-107]. Thus, sleep has emerged as a promising intervention target, not only to ameliorate suffering secondary to sleep disturbances, but also painful symptoms and a multitude of comorbidities. Interestingly, chronic pain not only seems to place the affected individual's health at risk, but, mediated through impaired sleep quality, also the spouse's [108].

Besides the recommendations for future research that have already been outlined, it is warranted to expand beyond the already examined clinical populations and conduct controlled PSG studies in other chronic pain conditions, such as CRPS, PHN and subtypes of chronic postsurgical pain. The use of PSG is especially salient, as compared to actigraphy or questionnaire methods, as PSG has the ability to evaluate whether disturbances in sleep architecture, as opposed to sleep continuity, contribute to varying effects of sleep disturbance on pain and related mechanisms. For example, some data indicate that inflammation contributes to hyperalgesia, and there is evidence that sleep depth as characterized by amount of slow wave sleep is associated with daytime levels of inflammation [109]. Similarly, amounts of REM sleep are also related to inflammation [21]. Hence, PSG studies that are combined with assessment of putative mechanisms linking sleep and pain have the potential to reveal these relationships.

In closing, it is also important to note that larger sample sizes, and longitudinal study designs, examining effects of various treatment modalities would be of high value. Hence, future well-designed PSG studies are needed to better characterize pain-related sleep disturbances; to capture the dynamic relationships between pain and sleep; to understand the role of sleep disturbance in perpetuating chronic pain states; and to identify what aspects of sleep (i.e., sleep fragmentation vs. sleep depth) that might serve as targets for intervention to mitigate pain symptoms in chronic pain populations.

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Glossary of terms

AHI	apnea/hypopnea index
ArI	arousal index
BDNF	brain-derived neurotrophic factor
CNS	central nervous system
CRPS	complex regional pain syndrome
CWP	chronic widespread pain
EEG	electroencephalography
FM	fibromyalgia
HC	healthy controls
IL	interleukin
MFP	myofascial pain
NREM	non-rapid-eye-movement
NSM	non-sleep migraine
OA	osteoarthritis
PHN	postherpetic neuralgia
PLMS	periodic limb movements during sleep
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
RA	rheumatoid arthritis
REM	rapid-eye-movement
RLS	restless legs syndrome
SE	sleep efficiency
SM	sleep migraine
SOL	sleep onset latency
SWS	slow-wave sleep
TIB	time in bed
TMD	temporomandibular disorders
TNF	tumor necrosis factor
TST	total sleep time
TTH	tension-type headache
WASO	wakefulness after sleep onset

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Practice Points

- There is no consistent pattern of objective sleep disturbances in nonmalignant chronic pain populations.
- Sleep continuity disruption, i.e., fragmentation of sleep, is the most common alteration of sleep found in chronic pain populations. Although increased amounts of superficial sleep, and decreased levels of slow-wave sleep, are found in a number of studies, sleep architecture is commonly preserved.
- The observed disturbances of sleep continuity suggest alterations in sleep stability, and deregulation of the homeostatic processes underlying sleep and wakefulness in patients suffering from chronic pain.
- Several comorbidities and pharmacological treatments associated with chronic pain states influence sleep.

Research Agenda

- Future PSG studies should expand beyond the already examined chronic pain populations.
- To ensure reliable results, several fundamental confounding factors should be taken into consideration when designing controlled PSG studies: adaptation night, careful matching of groups, sleep-influencing medications, and psychopathologies. Primary sleep disorders should always be screened for.
- Comprehensive qualitative and quantitative measures are necessary to facilitate analyses of correlations between subjective and objective sleep and pain parameters.
- Ideally, more than two nights should be recorded, since only sleeping two nights in a sleep laboratory might be insufficient to reflect the true variability of sleep in chronic pain patients. Longitudinal study design is encouraged. To facilitate recording of sleep continuity variables over extended time periods, use of actigraphy devices, in conjunction with sleep diaries, is recommended.
- Given the presented results, sleep continuity disruption models might best simulate the sleep disturbances of chronic pain patients. To date, there is a paucity of sleep deprivation studies in clinical chronic pain samples. Future research efforts examining pain populations are warranted, but ethical issues require consideration.
- Research directed toward unraveling the mechanisms underlying the bidirectional relationship between sleep and pain should be prioritized. Pivotal mechanisms include descending pain modulatory pathways and central neuroimmune activation.

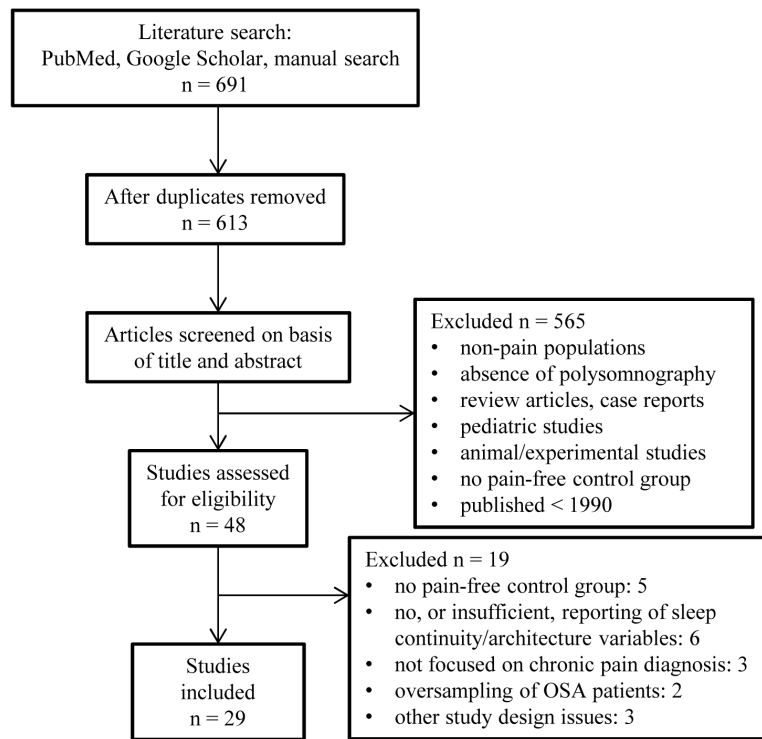


Figure 1. Flow chart of the study selection process

Abbreviations: OSA=obstructive sleep apnea.

Table 1

Sleep stages overview.

Wakefulness	Predominant alpha (8-13 Hz) and beta (>13 Hz) EEG activity.
NREM sleep	
Stage 1 / N1	The lightest sleep stage. Constitutes the transition between wakefulness and sleep. Predominantly characterized by low-voltage, mixed frequency background EEG activity (theta waves, 3-7 Hz). Typically lasts only about 5-10 minutes. During this stage the heart rate decreases, and the eyes exhibit slow rolling movements.
Stage 2 / N2	The majority of a night's sleep is spent in N2 (40-50%), characterized by background theta waves, less than 20% delta activity, and the occurrence of sleep spindles and K complexes. Eye movements usually disappear and muscles relax.
Stage 3 + 4 / N3 / SWS	Deepest sleep stage, identified by high-amplitude ($75 \mu\text{V}$), low frequency (<2 Hz) delta waves.
REM sleep	Characterized by low-voltage, mixed-frequency background activity, high brain activity, low muscle tone, and random movement of the eyes. In human adults, REM sleep occupies about 20-25% of sleep.

Abbreviations: EEG = electroencephalography, NREM = non-rapid-eye-movement, REM = rapid-eye-movement, SWS = slow-wave sleep

Table 2

Overview of controlled polysomnography studies in nonmalignant chronic pain populations.

Authors, year, ref #	Pain Population	N	M:F	Age	Controls	Pain Duration (years)	Medications
Abdulaziez and Asaad 2012 [68]	ankylosing spondylitis	20	20:0	37.8	HC, age-/gender-matched(n=10)	13.1	no comments
Anch et al 1991 [35]	FM	9	3:6	36.9	HC, age-/gender-matched(n=11)	NI	no meds used 14 days prior to PSG
Blagestad et al 2012 [86]	mixed	24	2:22	67.1	age-matched, pain-free, no hypnotics/antidepressants/analgesics, no sleep problems(n=19)	>2	pain group: 11 pts used hypnotics, 5 antidepressants, 18 analgesics
Branco et al 1994 [37]	FM	10	1:9	48	HC, ethnicity-matched(n=14)	5.3	no comments
Burns et al 2008 [45]/ Chervin et al 2009 [46]	FM	15	0:15	43.7	HC, age-/gender-/BMI-/menopausal status-matched(n=15)	NI	all psychotropic, hypnotic, analgesic meds discontinued 14 days prior to PSG
Carette et al 1995 [38]	FM	22	1:21	43.8	HC, age-/gender-matched(n=9)	6.9	hypnotics and NSAIDs discontinued >14 days prior to PSG; antidepressants discontinued >1 month prior to PSG
Côté and Moldofsky 1997 [39]	FM	10	0:10	32	HC, age-/gender-matched(n=9)	6.2	no meds were taken (washout period not mentioned)
Drewes et al 1995 [49]	FM	12	0:12	45.6	HC, age-/gender-matched(n=14)	6.9	all psychotropic drugs discontinued 14 days prior to PSG
Drewes et al 1998 [63]	RA	41	11:30	53.2	HC, age-matched(n=19)	13.5	no antidepressants, benzodiazepines 14 days prior to PSG; RA: 26 pts used second-line agents, 32 analgesics, 8 steroids
Dubrovsky et al 2014 [81]	TMD w chronic MFP	124	0:124	40.3	dental clinic pts (no TMD w MFP), age-, gender-, ethnicity-, socio-economic status-matched(n=46)	10.5	no restrictions
Engstrom et al 2014 [77]	migraine, TTH	73	21:52	38.9	HC, age-matched(n=34)	20	analgesics, triptans not discontinued; no comments about hypnotics, other sleep-influencing drugs
Gonzalez et al 2011 [51]	FM	32	0:32	50.1	HC, age-/gender-matched(n=20)	>2	no sleep-influencing meds
Hirsch et al 1994 [62]	RA	19	1:18	47.6	HC, age-matched(n=19)	10.6	no sleep-influencing drugs >14 days prior to PSG; RA: 13 pts used second-line agents, 3 steroids, 13 NSAIDs
Horne and Shackell 1991 [34]	FM	11	6:5	30	HC, age-/gender-matched(n=15)	NI	no analgesics or hypnotics
Jennum et al 1993 [36]	FM	20	0:20	45.6	HC, age-/gender-matched(n=10)	7.25	pts taking drugs other than analgesics were excluded
Karthik et al 2013 [76]	migraine	30	6:24	33.5	HC, age-matched(n=32)	5.2	sleep-influencing drugs stopped on the day of PSG; antimigraine prophylactic drugs discontinued >1

Authors, year, ref #	Pain Population	N	M:F	Age	Controls	Pain Duration (years)	Medications
Landis et al 2004 [44]	FM	33	0:33	45.4	HC, age-/gender-/BMI-/physical activity-matched(n=37)	NI	month prior to PSG no antidepressants, hypnotics, psychotropic meds > 14 days prior to PSG; pts taking steroids excluded
Lavigne et al 2011 [48]	CWP	24	11:13	44.1	HC, age-/gender-matched, pain-free, no sleep problems(n=24)	>0.25	no medication washout; no regular opioid use; CWP: 9 pts used NSAIDs, 15 antidepressants/hypnotics, 6 antihypertensive/cardiac meds, 3 HRT/thyroid meds
Leigh et al 1988 [73]	OA	14	14:0	63	HC, age-/gender-matched(n=16)	NI	psychotropic drugs discontinued 6 weeks prior to PSG; all other meds allowed
Leventhal et al 1995 [50]	FM	8	1:7	46	HC(n=7), generalized musculoskeletal pain(n=8) - all age-/gender-matched	NI	no tricyclic antidepressants, benzodiazepines, cyclobenzaprine 14 days prior to PSG
Mork et al [53]	FM	23	0:23	52.3	HC, age-/gender-/BMI-matched(n=22)	NI	hypnotics, analgesics discontinued 2 days prior to PSG
Okura et al 2008 [52]	CWP	17	9:8	54.8	insomnia(n=10), RLS/PLMS(n=10), HC(n=10) - all age-/gender-matched	NI	no opioids 7 days prior to PSG; no other modification of drugs; CWP: 6 used NSAIDs, 3 hypnotics, 6 muscle relaxants, 6 antidepressants, 5 antihypertensive meds
Rizzi et al 2004 [43]	FM	45	3:42	52.2	HC, age-/gender-/BMI-matched(n=38)	7.8	14 day washout period "for any pharmacological treatment related to FM"
Roehrs et al 2013 [47]	RA, FM	34	0:34	49.9	HC, age-/gender-matched, pain-free, no sleep problems(n=16)	NI	no antidepressant meds; no sleep-interfering meds; no pain meds 7 days prior to PSG
Roizenblatt et al 2001 [42]	FM	40	0:40	46	HC, age-/gender-/BMI-/menopausal status-/education level-matched (n=43)	5	pts w regular intake or abuse of sleep-interfering meds excluded
Rossetti et al 2008 [84]	TMD w chronic MFP	30	6:24	26.6	HC, age-, gender-matched(n=30)	2.9	no sleep-influencing meds
Schneider-Helmert et al 2001 [85]	mixed	26	12:14	46.4	chronic primary insomniacs, age-matched, pain-free(n=25)	>0.5	all chronic pain pts + controls spontaneously free of any meds > 4 weeks prior to PSG
Sergi et al 1999 [41]	FM	17	1:16	51.2	HC, age-/gender-/BMI-matched (n=17)	4.7	sleep-influencing meds discontinued 14 days prior to PSG
Shaver et al 1997 [40]	FM	11	0:11	43.8	HC, age-/gender-/BMI-/menopausal status-matched(n=11)	NI	no psychotropic, sedative, hypnotic meds

Abbreviations: BMI=body mass index, CWP=chronic widespread pain, FM=fibromyalgia, HC=healthy controls, HRT=hormone replacement therapy, LBP=low back pain, meds=medications, MFP=myofascial pain, misc=miscellaneous, NI=not implemented, OA=osteoarthritis, pt(s)=patient(s), PLMS=periodic limb movements during sleep, PSG=polysomnography, RA=rheumatoid arthritis, ref=reference, RLS=restless legs syndrome, sig=significant, TMD=temporomandibular disorders.

Table 3

Summary of main macro- and microstructure sleep parameter findings: chronic pain condition vs control group(s).

Chronic Pain Condition	Sleep Continuity	Sleep Architecture	AHI, ArI, PLMS index	EEG Power Spectral Analysis; visually scored alpha and delta ratings
Fibromyalgia & CWP	TST ↓ [41,43,47,48,51-53] SOL ↑ [34,38,44,48,53] SE ↓ [41,43,44,48,49,52,53] WASO ↓ [47,49,51] #awakenings ↑ [36,37,48,51] no sig diff [35,36,39,40,45/46,50] no group comparisons [37,42]	N1 ↓ [35,50] N1 ↑ [39,41-44,49] N2 ↓ [37,44] N2t [51] N3 ↓ [41,43]; N3(S4) ↓ [37,51] REM ↓ [35,37] #sleep stage shifts ↑ [45/46] #sleep cycles ↓ [48,52] no sig diff [34,36,38,40,47]	ArI ↑ [36, 41, 43] PLMS index ↑ [51, 52] no sig diff [42,45/46,48] group comparisons not reported [36,37,39,40,44,47,49] NI [34,38]	alpha power N3 ↑ [38] alpha power N2+N3 ↑ [42,49] delta power N2+N3 ↓ [49] alpha/delta-ratio ↑ (all sleep cycles) [37] alpha power no sig diff [34,45/46,48] NI [35,36,39-41,43,44,47,50-53]; alpha ratings N3 ↑ [38,43] alpha ratings N2+N3 ↑ [35,42] visual scoring no sig diff [39,40,50,51] no group comparisons [41] NI [34,36,44-49,52,53]
Rheumatoid arthritis	TST ↓ [47] SOL ↑ [62] SE ↓ [62] WASO ↑ [47,62] #awakenings ↑ [62] no sig diff [63]	no sig diff [47,62,63]	PLMS index ↑ [63] no group comparisons [47,62]	alpha power N2+N3 ↑ [63] NI [47,62]; no group comparisons [62] NI [47,63]
Ankylosing spondylitis	SOL ↑ [68] SE ↓ [68]	N1 ↑ [68] N2 ↑ [68] N3 ↑ [68]	ArI ↑ [68] PLMS index ↑ [68] (but within normative levels)	NI [68]; NI [68]
Osteoarthritis	no sig diff [73]	N1 ↑ [73] N2 ↓ [73]	NI [73]	NI [73]; NI [73]
Migraine and TTH	SOL ↑ [76] SE ↓ [76] WASO ↑ [76] #awakenings ↑ [76,77]	N3(S4) ↓ [76] N3 ↑ (TTH, NSM) [77] total NREM sleep ↓ [76]	ArI ↓ [76] no group comparisons [77]	NI [76,77]; NI [76,77]
TMD w MFP	no sig diff [81, 84]	N1 ↑ [81] no sig diff [84]	no sig diff [81] no group comparisons [84]	NI [81, 84]; NI [81, 84]
Mixed chronic pain conditions	SE ↓ [86] WASO ↑ [86] #awakenings ↑ [86] no sig diff vs insomniacs [85]	no sig diff vs insomniacs [85] no sig diff [86]	no group comparisons [85] no sig diff [86]	alpha power no sig diff [85,86] delta power ↓ throughout night [86]; NI [85,86]

Abbreviations: ↑=increased, ↓=decreased, #awakenings=number of awakenings, #sleep cycles=number of sleep cycles, AHI=apnea-hypopnea index, ArI=arousal index, CWP=chronic widespread pain, diff=differences, MFP=myofascial pain, NI=not implemented, NSM=non-sleep migraine, N1=NREM stage 1, N2=NREM stage 2, N3=NREM stage 3, PLMS=periodic limb movements during sleep, S4=stage 4, SE=sleep efficiency, SM=sleep migraine, SOL=sleep onset latency, TMD=temporomandibular disorders, TST=total sleep time, TTH=tension-type headache, WASO=wakefulness after sleep onset.