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Sleep Disturbance and Nonmalignant Chronic Pain: A Comprehensive Review of the Literature

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ABSTRACT

Sleep disturbance is an important clinical complaint for individuals with nonmalignant pain conditions. This review is a broad introduction to the literature on sleep disturbance and chronic pain conditions. The article critically reviews studies of sleep disturbance in musculoskeletal pain, arthritis, headache, and fibromyalgia. Current neurobiological hypotheses regarding the pathogenesis of sleep disturbance and chronic pain, common comorbid disorders, and pharmacologic and non-pharmacologic treatments for sleep disturbance are reviewed.

Key Words. Chronic pain; Sleep quality; Sleep disorders

Introduction

Overview

Sleep disturbance is a prevalent clinical complaint among persons with chronic pain conditions. Although difficulties initiating and maintaining sleep are common within the general population, the prevalence within the pain population is striking. Recent estimates of sleep disturbance show that approximately 10% of primary care patients in the United States report major current insomnia as determined by the Composite International Diagnostic Interview [1]. A survey of 1,722 Canadian residents found similar trends within the general population. In this study, 17.8% reported dissatisfaction with sleep, and 10.8% of people classified their sleep disturbance as frequent or very frequent [2]. In contrast to these estimates, levels of sleep disturbance measured in smaller clinical samples of pain patients range from 50% to 70% [2,3].

Pain is one of the most common reasons patients seek medical care. A survey of 1765 Australian residents found pain to be the most significant factor in determining poor sleep [4]. Common sense dictates that it is difficult to initiate and maintain sleep while experiencing a painful stimulus. Thus, sleep disturbance in the context of a pain condition has been attributed to the pain itself. However, evidence from animal models and human investigations indicates a complex relationship between pain and sleep disturbance [5,6]. The purpose of this article is to provide a critical review of the literature on pain and sleep, with a focus on the most researched nonmalignant pain conditions (ie, unspecified chronic pain, arthritis, headache, and fibromyalgia). In addition, current neurobiological hypotheses about the pathogenesis of sleep disturbance and chronic pain, common comorbid disorders, and pharmacologic and nonpharmacologic treatments for sleep disturbance will be reviewed.

Sleep characteristics and measurement tools

Both subjective and objective measures are used to quantify sleep disturbance. Most commonly, researchers study objective sleep physiology using polysomnography. A polygraph machine records change in bioelectric potentials using electrodes placed on the skin of the scalp and face. An electroencephalogram (EEG), measuring brain waves; an electro-oculogram (EOG), measuring eye movements; and an electromyogram (EMG), measuring muscle activity are recorded using the polygraph machine. Once a tracing is produced it is analyzed, and sleep is categorized into stages according to standard criteria [7].

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Sleep is divided into 5 stages: stages 1, 2, 3, 4, and REM (rapid eye movement). During wakefulness, the EEG is characterized by alpha activity and/or low voltage, mixed frequency activity. Stages 1, 2, 3, and 4 are considered non-REM (NREM) sleep. Stages 3 and 4 are characterized by a predominance of high voltage delta waves. For this reason, stages 3 and 4 often are called, collectively, delta sleep or slow wave sleep. Relatively low voltage, EEG mixed frequencies, and rapid eye movement characterize REM sleep, also called paradoxical sleep [8].

Actigraphy is another method for objective sleep monitoring that measures the sleeper's activity during the night and day. A movement sensor is placed on the patient's wrist or ankle and translates movements into a digital code that is stored in computerized form. This technique is particularly useful because it does not require that patients sleep in a sleep laboratory and measurements can be taken continuously for a week or more [9]. The actigraph distinguishes between sleep and wakefulness, and is purported to measure sleep quantity and quality [10]. However, this method is limited in that it does not distinguish between true sleep and motionless periods of wakefulness. Artifacts related to movements made while breathing, or to aspects of the device (eg, device sensitivity, device placement), can affect the reliability of actigraphy [11]. Additionally, some studies show actigraphy is no more accurate than daily sleep logs in estimating sleep latency [12]. Therefore, there is currently some debate as to whether actigraphy is a valid tool for use in a research setting. The use of two actigraphs, one placed on the dominant hand and one placed on the nondominant hand, may enable identification of artifacts due to breathing and improve measurement validity [10].

Several self-report measures describe subjective sleep quality and quantity. Two popular methods are sleep diaries [13], in which patients record their sleep habits on a daily basis, and sleep questionnaires (eg, The Pittsburgh Sleep Quality Index; PSQI) that require retrospective assessment of sleep quality [14]. Sleep diaries generally require patients to record times of sleep during both night and day. Additionally, sleep latency, total hours of sleep, number of awakenings, daytime sleepiness, and medication intake are recorded for the period of study. Patients are fairly reliable in assessing their total sleep time and sleep efficiency through sleep diary recordings, but tend to overestimate sleep onset latency and underestimate the number of awakenings they experienced each night [15]. Questionnaire methods involve one-time retrospective reporting of sleep disturbances. The validity of the PSQI was found by discrimination from controls and through positive correlations with polysomnography [14]. The PSQI was correlated with polysomnography for sleep latency, but not for estimates of sleep duration and sleep efficiency [14]. Other questionnaires (eg, The Sleep Disorders Questionnaire) have been designed to detect symptoms of sleep disorders and have shown sensitivity and specificity [16]. This type of questionnaire is generally recommended to enhance screening efforts of primary practitioners [16]. Several of the above methods may be used to give a complete view of a patient's sleep quality.

There are strengths and limitations with all types of measurement. The gold standard of measurement of sleep disturbances is polysomnography. Expense and the time involved limit this method of investigation for most studies. Additionally, sleep researchers generally require that patients not take CNS-active medications for 2 weeks prior to a sleep study. This requirement is a stringent one and can be a limitation for many individuals treated for pain conditions. Actigraphy involves more resources than questionnaires, but may yield better estimates of sleep onset latency and number of awakenings. Diary or questionnaire methods are inexpensive and easily administered and may be a beginning assessment tool for practitioners prior to employing more expensive and thorough methods of assessment.

Sleep Disturbance and Nonmalignant Pain Conditions

Sleep disturbance in the chronic pain population

Sleep disturbance has been documented in studies of individuals referred to pain clinics. Although their diagnoses may differ, the most prevalent complaints of pain are low back and cervical. One fact is consistent in the literature: chronic pain patients report a significant amount of sleep disturbance. The relationship between pain intensity and sleep disturbance may be complicated, however, by mood disturbance and by the limitations of self-report measures of sleep.

In a study of 100 individuals referred to a multidisciplinary outpatient chronic pain clinic, 70% reported "poor" sleep, while another 20% reported "fair" sleep [3]. Poor sleepers were differentiated from better sleepers by fewer hours of sleep, more hours spent reclining during the day, more disability, and greater ratings of pain intensity. Additionally, individuals who reported more sleep disturbance endorsed significantly higher scores on measures of depression and anxiety [3]. A similar,

but more recent study of 100 patients referred to a multidisciplinary pain clinic found that 65% described themselves as "poor sleepers" [17]. When compared to individuals who classified themselves as "good sleepers," individuals who rated themselves "poor sleepers" reported longer latency to fall asleep, more frequent awakenings, longer duration of awakenings, and fewer total hours of sleep. Additionally, "poor sleepers" described greater pain intensities. No difference in mood was found between "good" and "poor" sleepers when mood was measured by a visual analog scale (VAS) [17]. Pain duration and depressed mood predicted sleep satisfaction in a study of 51 patients referred to an outpatient orthopedic clinic, where approximately 50% of the sample reported sleep disturbance [2].

Haythornthwaite et al. [13], found similar results in a study of 46 individuals (85% males) referred to an inpatient rehabilitation pain program. Patients maintained sleep diaries for an average of 5 days. Pain-related variables (eg, the duration of pain and pain intensity) were significantly positively correlated with delayed sleep onset, lower quality of sleep and fewer hours slept. Sleep disturbance, as measured by sleep diary items, was positively correlated with measures of depression and anxiety [13]. Wilson [15] documented the presence of insomnia using sleep diaries and actigraphy. He found that pain severity was associated with disturbed sleep using the diary, but not actigraphy, for individuals reporting high pain severity.

There are few polysomnographic studies of patients with chronic pain conditions. In the largest study found to date, Wittig et al. [18] compared polysomnographic recordings of 26 patients with chronic pain to 12 patients with insomnia and psychiatric disorder, and 16 patients with insomnia with no objective findings. The results revealed that patients with chronic pain had evidence of disturbed sleep efficiency (ie, the total sleep time/time in bed), and increased wake time during the night and before sleep, compared to individuals with subjective insomnia. Eight of the individuals with chronic pain showed the presence of alpha rhythm intrusion on the EEG in non-REM (NREM) sleep. Wittig et al. [18] suggest that pain tolerance decreases with lack of sleep and may partially account for reports of increased pain perception.

Although these studies provide evidence that individuals with chronic pain experience sleep disturbance, few studies use objective measures of sleep disturbance or standardized questionnaires. Characterization of sleep disturbance should move beyond classification of individuals as self-described "good" and "poor" sleepers. One difficulty in integrating the results of these studies is the variety of populations studied. Individuals who present to an outpatient orthopedic practice are likely different from inpatients with chronic pain. Further specification of demographic and diagnostic categories in the populations studied is needed to form generalizations about sleep and pain in this population. Another difficulty with these studies is the lack of information on the types of medications taken by patients. Individuals with chronic pain conditions may be taking serotonin-selective reuptake inhibitors (SSRIs), which have been shown to cause insomnia in some individuals. Reporting of sleep difficulties may also be obscured if study participants are taking other, more sedating medications, such as tricyclic antidepresssants, opioids, or muscle relaxants.

Sleep disturbance in rheumatic diseases and arthritis

Individuals with arthritic conditions commonly report sleep dysfunction. In fact, pain secondary to arthritis was the most significant factor in predicting sleep disturbance in a large survey of Australian residents [4]. Sleep disturbance in the rheumatic diseases has been most studied in persons with rheumatoid arthritis (RA). In a survey of 242 patients with rheumatoid arthritis, 60% reported that arthritis pain interfered with sleep to some degree, with an additional 14% reporting severe or very severe interference [19]. The nature of sleep disturbance in an outpatient sample of 100 persons with rheumatoid arthritis was found to include both insomnia (34%) and middle-of-the-night awakening (52%) [20]. Lavie et al. [21] found sleep quality, as measured by actigraphy, was more disturbed for persons with RA, compared to healthy controls and patients with low back pain.

Polysomnography has been used in an animal model of adjuvant arthritis, showing increased wakefulness and marked sleep fragmentation in arthritic rats compared to control rats [5]. Additionally, there were positive correlations between severity of arthritis and percentage of time spent in non-rapid-eye-movement (NREM) sleep with low and moderate amplitude. The results of this experiment suggested that arthritic rats cannot sustain long periods of sleep and that the low EEG amplitude found in the arthritic rats may be related to disease severity, to a correlate of disease severity (eg, pain) or to a deficit of EEG-generating mechanisms [5].

Sleep fragmentation was found in a study of 16 male rheumatoid arthritis patients who underwent polysomnography [22]. Participants showed no ob-

jective evidence of sleep deprivation, marked disturbances in arousal, or frequent movement of extremities; and two individuals were diagnosed with sleep apnea. Participants failed to recognize the degree of their sleep disturbance on self-report questionnaires, although daytime sleepiness, measured by the multiple sleep latency test (MSLT) [23], was documented [22].

In 14 men with osteoarthritis, and 16 age- and gender-matched controls, polysomnography revealed more stage 1 sleep and less stage 2 sleep in the patient group [24]. The authors concluded that continuation of nonsteroidal anti-inflammatory (NSAID) and analgesic medications may have obscured more significant differences between the groups. There is additional evidence, however, that pain is not the only significant contributor to sleep dysfunction in patients with rheumatoid arthritis. Lavie and colleagues [25] found that although the NSAID tenoxicam made significant improvements in all clinical parameters of 13 RA patients, sleep was not improved. In fact, primary sleep disorders were found in 8 of the 13 patients.

Few studies of sleep disturbance document the prevalence and nature of sleep disturbance in other rheumatic diseases. One exception is a recent study of patients with primary Sjogren's syndrome. Tishler et al. found that 75% of patients experienced moderate to severe sleep disturbance, significantly higher than individuals from 3 rheumatologic comparison groups [26].

Very little is known about the extent of specific sleep difficulties in rheumatic diseases or the extent to which sleep disturbance affects the quality of life. None of the studies reviewed used standardized self-report measures of sleep disturbance. Polysomnographic studies have found primary sleep disorders in some participants. However, these results are tempered by the fact that study participants were primarily men, in whom some sleep disorders are more common.

Sleep disturbance in headache

The most common pain syndrome occurring in the general population is headache. The most frequent types of headaches are migraine, cluster, tension-type and paroxysmal hemicrania [27]. Significant numbers of patients who suffer from headaches also experience sleep disturbance [28–30]. Both inadequate and excessive amounts of sleep have been implicated in the causation of headaches [31].

Phase differences in sleep have been shown for individuals with different types of headache. Patients with migraine headaches have been found to exhibit an excessive percentage of stages 3, 4, and REM sleep [32]. However, other investigators found that persons with migraine had normal sleep, as documented by an ambulatory EEG monitoring device, with the exception that REM sleep and REM latency were increased compared to individuals with tension or tension-vascular headaches [29]. Individuals with tension headache exhibited a variety of sleep disturbance characteristics (eg, reduced sleep time and efficiency, decreased sleep latency, frequent awakenings, increased nocturnal movements, and a reduction in slow wave sleep) compared to individuals with migraine or tension-vascular headache [29]. Additionally, there is some polysomnographic evidence that nocturnal cluster headaches occur during REM sleep [33,34].

Some headache symptoms have been relieved by sleep deprivation, a finding that further supports a link between sleep and headache. Because cluster headaches tend to occur during REM sleep, an attempt to minimize or delay REM sleep in these patients has been tested therapeutically. Depriving cluster headache patients of sleep prevented headaches for 24 hours in 14 of 27 patients and reduced headache frequency for the entire group during the next 4 days [35].

Sleep disorders may complicate the relationship between headaches and sleep. A study comparing patients with persistent psychophysiological insomnia (PPI), with patients with dysthymic disorder and normal subjects, found that PPI patients displayed more tension-related symptoms, including headaches [36]. Pavia et al. [37] found that 10% of individuals referred to a headache clinic had diagnosable sleep disorders, primarily periodic limb movements, and sleep apnea. Treatment of the sleep disorder alleviated or reduced headache complaints. Moreover, a significant increase in sleep-related complaints was found among individuals with headache with and without a comorbid sleep disorder. Individuals with sleep disorders endorsed more daytime sleepiness, nocturnal sleep disturbance, shortness of breath when waking up, sleep walking, and sleep paralysis at the onset of sleep, than individuals with headache and no existing sleep disorder [37].

Clearly, many headache syndromes have a relationship with sleep. The exact nature of that relationship varies significantly with the type of headache, and in many cases it is unclear which disorder is the primary causative illness. Though common electrophysiologic, anatomic, and biochemical substrates appear to exist between sleep and headaches, the exact relationship has yet to be determined [33].

Sleep disturbances in fibromyalgia

Fibromyalgia has been called neurasthenia, psychogenic rheumatism, hysteria, and masked depression [38], indicating the presence of psychiatric symptomatology, and is now named fibromyalgia syndrome, fibrositis, or diffuse myofascial pain syndrome by the International Association for the Study of Pain (IASP) [39]. The pathophysiology of the condition, which is characterized by chronic musculoskeletal pain, nonrestorative sleep, chronic fatigue, early morning stiffness and specific tender points, is currently unknown [40]. Sleep dysfunction is considered an ancillary feature of the condition, since a large percentage of fibromyalgia patients experience both subjective and objective sleep disturbances. The percentage of persons with fibromyalgia who report sleep disturbances ranges between 62% and 75.6% compared to ranges between 9% and 31.1% for healthy controls [40,41].

Considerable controversy exists as to whether fibromyalgia should be considered a diagnostic entity. Critics of labeling the constellation of symptoms as a diagnostic syndrome point out the dangers in diagnosing individuals with fibromyalgia when their symptoms probably fall within a bell-shaped curve of normal physiologic responses to internal and external stimuli. Some have charged that this labeling constitutes iatrogenic illness that encourages illness behaviors [42,43]. Many of the studies reviewed in this paper have been performed with individuals with fibromyalgia, which is a reflection of the available literature on sleep and pain. Therefore, these studies should be interpreted with some caution.

Moldofsky and his colleagues described the presence of an EEG sleep anomaly, a wave form known as alpha-delta sleep, that corresponds with the nonrestorative sleep experienced by fibromyalgia patients [44]. Alpha-delta sleep is thought to intrude upon NREM sleep and cause the patient to awaken feeling unrefreshed and tired. Alpha intrusion has also been reported in other pain disorders, most notably rheumatoid arthritis [22,45]. However, study samples are small and the phenomenon has not been widely replicated in other studies. Several theories regarding the relation between the alpha-delta EEG sleep anomaly and chronic pain syndromes will be discussed later in the paper.

Fibromyalgia shares several clinical symptoms with chronic fatigue syndrome, including non-restorative sleep, musculoskeltal pain, and fatigue. EEG abnormalities have been shown for patients with chronic fatigue syndrome, most notably delayed sleep onset, decreased REM sleep and increased alpha activity during NREM sleep [46].

Comorbid Primary Sleep Disorders

The presence of comorbid primary sleep disorders, other than insomnia, in persons with chronic pain conditions has been found by several investigators [25,42]. There is a striking lack of research focused solely on this phenomenon. However, the nature of the relationship needs to be elucidated in order to determine an appropriate treatment plan. Sleep apnea, restless legs syndrome, and periodic limb movements in sleep (nocturnal myoclonus) are the most commonly cited ailments that may have an association with pain conditions.

Sleep apnea

Obstructive sleep apnea (OSA) has been found in several studies of individuals with chronic pain conditions. A study of 13 female rheumatoid arthritis patients found that 8 had a primary sleep disorder as documented by polysomnography [25]. Patients in this study had either periodic limb movements in sleep, sleep apnea, or both. Other investigators have shown the presence of OSA in persons with RA [22].

Molony et al. [47] studied 11 patients diagnosed with sleep apnea and found that 3 individuals met criteria for fibromyalgia. Although frequent arousals during sleep were present in a comparison sample of individuals with fibromyalgia, no sleep apnea was found. The investigators proposed that some individuals with symptoms of fibromyalgia might have a sleep apnea syndrome. Distinguishing these disorders is critical in treatment, since some medications that are used to treat fibromyalgia are CNS depressants and might be relatively contraindicated for individuals with sleep apnea [47].

Sleep apnea and other respiratory disorders have also been associated with headache, although the numbers of patients studied is very small. For example, sleep apnea was found in 3 of 18 chronic headache patients. Nocturnal headaches were positively correlated with oxygen desaturation, whether or not sleep apnea was present [37]. Individuals with chronic nocturnal headaches report more sleep abnormalities, such as oxygen desaturation and sleep apnea, than individuals in the normal population [32,48]. The prevalence of sleep apnea patients who experience early morning headaches leads to speculation that hypoxic interludes during apnea, especially during REM sleep, may trigger cluster headaches.

Periodic limb movements/restless legs syndrome

Periodic limb movements have been found in polysomnographic studies of RA patients. In one inves-

tigation, all (N = 13) patients revealed frequent movement of extremities and frequent arousals during sleep. Additionally, 10 patients showed abnormal extremity movements during wakefulness, which appeared to interfere with sleep onset and return to sleep [22]. A mean of more than 40 episodes of periodic leg movements were found in another investigation of individuals with RA. Evidence for the presence of periodic leg movements has been found for individuals with chronic pain conditions [18]. Atkinson et al. [2] performed polysomnography for 7 patients with chronic low back pain and found the majority of patients met criteria for periodic limb movements in sleep. Additionally, Moldofsky proposed that the prevalence of myoclonus in fibrositis patients warranted a subcategory of the syndrome to include this sleep disorder [49].

Although preliminary evidence suggests that some individuals with chronic pain conditions can also be diagnosed with a sleep disorder, small samples and uncontrolled research make generalizations difficult. Further research should be conducted on comorbid sleep disorders. Practitioners might increase the frequency with which they screen for primary sleep disorders.

Mood Disturbances Associated With Pain And Sleep Disorder

Depression, anxiety, and fatigue are all implicated in a complex pain/sleep relationship. Since fibromyalgia has historically been associated with psychiatric illness and sleep disturbance, much of the available literature focuses on this syndrome. Since the diagnosis of fibromyalgia is controversial, some caution should be used in interpreting these studies. There is some research accumulating, however, which links symptoms of mood disturbance, pain, and sleep in other chronic pain populations.

Depression

A large literature documents the presence of depression in persons with chronic pain conditions [50–52]. Additionally, there is a well-established history of sleep disturbance in patients suffering from depression. Depressed patients experience frequent awakenings, longer sleep latencies, and REM abnormalities [53,54]. Although no causal relationships have been documented, several studies focus on the interrelationships between pain, depression, and sleep that complicate diagnosis and treatment.

Persons diagnosed with fibromyalgia report higher psychological symptomatology, including depression and anxiety, than healthy controls [55,56]. Some studies have shown a greater degree of psychological distress in fibromyalgia compared to other chronic pain conditions [57]; however, the role that psychological factors play in the etiology of fibromyalgia remains controversial. Ahles et al. [58] found no support for a psychopathology model in the etiology of fibromyalgia. Additionally, differences in sleep physiology were found between persons with dysthymic disorder and persons with fibromyalgia, providing some support for the separation of these diagnoses [59]. However, the presence of mood symptomatology in this population continues to be an enduring clinical complaint. A 7-year treatment outcome study of 538 patients in several rheumatology clinics specializing in the treatment of fibromyalgia, found measures of depression, anxiety and sleep disturbance relatively unchanged over the period of the study. No specific information about treatment for these symptoms was given, except that the authors noted that behavioral treatments were not provided [60].

Other research has provided some insight into the relationship between depression, pain, and sleep for individuals with RA. Nicassio and Wallston [19] studied 242 persons with RA over a 2-year interval. Cross-sectional regression analyses revealed that sleep difficulties, measured by several questions, were independently associated with depression. However, longitudinal analyses revealed that pain at Time 1 predicted sleep difficulties at follow-up. An interaction of high pain and high sleep problems was independently associated with depression from the beginning of the study to follow-up. The authors suggest that pain exacerbates sleep disturbance and that, over time, both pain and sleep disturbance may be associated with depression [19].

Other correlational evidence links mood and sleep disturbance. Moldofsky found that the percent of alpha intrusion during non-REM sleep is positively correlated with pain, hostility and decreased mood [61]. Atkinson found depressed mood more strongly associated with sleep dissatisfaction than with evidence of orthopedic disease [2]. In contrast, another study demonstrates that pain frequency and intensity were stronger predictors of sleep disturbance than mood or personality [62]. Future research should focus on teasing out predictors of sleep, pain, and mood; and documenting effects of treatment targeting these variables.

One difficulty inherent in these studies is that measures of depressed mood are often laden with neurovegetative symptoms (eg, sleep disturbance, fatigue) that co-vary with sleep disturbance. Further, few studies exclude individuals with major depressive disorders.

Anxiety

Anxiety has been most studied in persons with fibromyalgia. Evidence for higher levels of anxiety disorders in persons with fibromyalgia is mixed. The lifetime prevalence of anxiety disorders, as measured by the Diagnostic Interview Schedule (DIS), was found to be higher for patients with fibromyalgia than for patients with RA [63]. However, no differences in lifetime history of psychiatric disorders, including anxiety disorders, were found between persons with fibromyalgia, RA, and persons without pain [58].

Studies measuring the presence of symptoms of anxiety also produce mixed results. Krag et al. [64] found higher levels of trait anxiety and melancholia reported by fibromyalgia patients, when compared to groups of individuals with RA and disc herniations, when pain intensity was controlled. In contrast, no statistical differences were found on measures of state and trait anxiety, depression, and other psychiatric symptomatology, between persons diagnosed with fibrositis and individuals without fibrositis who reported diffuse musculoskeletal pain and a nonrestorative sleep pattern [65].

Mediating factors may account for reported differences in anxiety and psychiatric symptomatology for individuals with fibromyalgia. For example, Aaron et al. [6] found that individuals with fibromyalgia who sought medical care reported significantly more psychological distress than individuals with fibromyalgia who did not seek treatment. However, differences in psychological distress, including anxiety, were eliminated after controlling for pain and fatigue [6]. Other investigators have found generalized anxiety and trait anxiety to be positively correlated with pain intensity [55,60].

Although the presence of anxiety has been shown to interfere with sleep, few studies have combined sleep disturbance, pain, and anxiety as a focus of study. Given the established relationships between chronic pain, sleep, and psychiatric symptomatology, the interactions between these variables are deserving of further study.

Fatigue

Belza [66] defines fatigue as "the enduring, subjective sensation of generalized tiredness or exhaustion (p. 639)." Fatigue is considered a symptom of some chronic pain conditions and is used as an index of disease activity in RA [67]. The absence of fatigue is one of 5 criteria used to document remission of RA [68]. Study of this aspect of chronic illness is complicated by the existence of few standardized measures. Fatigue has been positively correlated with higher ratings of pain and depression, poorer functional status, and disturbed sleep for individuals with RA [66]. A large study of patients with rheumatic disease found pain, sleep disturbance, and depression accounted for a large proportion (49%) of the variance in predicting fatigue, which was measured by a VAS scale from 0 to 3. Additionally, the model accounted for 45% of the variance for individuals with osteoarthritis, and 41% of the variance for individuals with fibromyalgia. Further, the authors concluded that the relationship between sleep disturbance and fatigue remained strong even when depression was taken into account [69].

Fatigue was measured using the Fatigue Severity Scale [70] in a study of 64 persons with fibromyalgia, 28 persons with FMS who did not present for medical care (nonpatients), and 23 healthy controls. Persons with FMS reported significantly more fatigue than nonpatients and healthy controls, while nonpatients reported significantly higher levels of fatigue than healthy controls [6]. Higher levels of fatigue were also found for patients with fibromyalgia compared to patients with RA and ankylosing spondylitis [71]. Existing data suggest that fatigue is a commonly reported symptom that co-varies with other important clinical symptoms associated with chronic pain and sleep disturbance, and deserves further investigation with standardized measures.

Neurobiological Hypotheses Regarding Pain and Sleep

Few current neurobiological hypotheses explain the complex relationship between chronic pain and sleep disturbance. Alpha wave intrusion into non-REM (NREM) sleep has been forwarded as a possible mechanism of sleep disturbance in persons with chronic pain conditions [44]. Additionally, sleep and pain may use common neurotransmitters.

Alpha-delta sleep

Alpha-delta sleep was first recognized as a distinct wave form in polysomnography by Hauri and Hawkins [72], and is characterized by 5% to 20% delta waves mixed with large amplitude alpha waves. Alpha-delta sleep was described as occurring early in the evening, and opposite REM sleep in the 90-minute sleep cycle when delta sleep is normally expected. The pattern correlated with reports of "a general feeling of chronic somatic malaise and fatigue" [72]. The alpha EEG sleep anomaly has been hypothesized to play a unique role in the interaction between pain and sleep.

Moldofsky and colleagues proposed that fibromyalgia patients experience a cycle of nonrestorative sleep, in which alpha waves intrude upon NREM sleep, that leads to the development of musculoskeletal symptoms [44]. In their initial study, 7 out of 10 fibromyalgia patients showed the alpha-delta pattern of sleep disturbance. The remaining 3, who did not show this disturbance, had negligible delta sleep. Six healthy individuals were then subjected to an auditory arousal stimulus during NREM sleep that caused the alpha-delta pattern. These healthy individuals subsequently reported musculoskeletal pain and mood disturbance similar to the symptoms reported by patients with fibromyalgia [44]. The healthy volunteers who underwent NREM sleep disturbance were compared with healthy volunteers with REM sleep deprivation. Results revealed that NREM sleep disturbance resulted in more complaints of musculoskeletal tenderness, which disappeared with 2 nights of undisturbed sleep [73]. Other studies [18,74–76] of individuals with fibromyalgia or musculoskeletal pain, compared to healthy controls, have confirmed the presence of alpha intrusions in NREM sleep, as well as abnormalities of sleep cycle organization.

Fibromyalgia patients differ from those patients who are merely experiencing sleep disturbance. They show an average of 60% duration of alpha rhythm during NREM sleep, compared with 25% for patients experiencing chronic insomnia [59]. The alpha-delta anomaly has been found to occur in healthy individuals as well. Scheuler et al. reported this anomaly in 6 of 44 healthy people and individuals taking benzodiazepines [77].

The amount of alpha intrusion may be positively correlated with pain and psychological distress. In a small study, patients with fibromyalgia were randomly assigned to groups comparing two drugs known to increase NREM sleep (chlorpromazine and L-tryptophan). Chlorpromazine, but not L-tryptophan, was associated with increased slow wave sleep and decreased pain and psychological distress. The mean percent of alpha frequency (intrusions) during NREM and REM sleep was associated with increased pain and decreased energy and mood [8].

Although alpha-delta sleep may be an indicator of fibromyalgia, and may affect symptoms such as pain and tenderness, it does not seem to be exclusive to this disease. Both morning stiffness [45] and fatigue [22] have been proposed as consequences of the presence of alpha-delta sleep for individuals with RA.

Although there appears to be a relationship between musculoskeletal pain and tenderness, and the alpha EEG sleep anomaly, data on the prevalence of this phenomenon is absent. The presence of the anomaly in individuals with pain, as well as healthy individuals, poses questions about its centrality to pathophysiologic mechanisms between pain and sleep disturbance. More research is needed regarding alpha intrusion in specific chronic pain groups such as back pain, RA, and headache in order to determine whether alpha intrusion is a core pathophysiologic issue or an epiphenomenon in the neurobiological connection of sleep disturbance and chronic pain.

Neurochemistry of pain and sleep disturbances

This section reviews some of the identified neurochemistry of sleep and highlights neurotransmitter systems that have possible roles in both sleep and pain. Syndromes involving chronic pain and fatigue have been described for centuries, with linking pathophysiology long-sought and elusive [78]. This current status results from the ubiquity of certain neurotransmitter systems in the human brain, the complexity of interactions between various neurotransmitter systems, internal and external influences on pain and sleep, involvement of inflammatory mediators, and deeper cellular events such as activation of secondary and tertiary messengers and gene transcription. The numerous and complex influences of neurochemistry on sleep and pain becomes more evident as new research emerges.

A long literature, nearly 30 years old, has focused on the roles of serotonin in non-REM sleep, pain modulation, and affective states [79–81]. The serotonergic system has the broadest projections to human cortex among the various known neurotransmitters [82], originating in the brainstem and raphe nucleus, and complicating the specific isolation of serotonergic influences in pain, sleep and depression.

In the descending modulation of anterolateral quadrant pain transmission, serotonin is involved in the dorsolateral funiculus that mediates pain transmission in the dorsal horn of the spinal cord. Various lines of evidence support an important role for serotonin in major depression, including studies of platelet serotonin, CSF serotonin, and postmortem studies of patients who died by suicide [83,84].

In the treatment of various chronic pain syndromes with SSRIs, serotonin has been suspected as critical to the mechanism of action of these agents for pain and/or depression. Various reports on SSRIs in the treatment of chronic low back pain, chronic abdominal pain, and pain syndromes where there are intrusive pain-related ideas and rituals, suggest an important mechanistic role for serotonin

[85–87]. Max suspected that serotonin was central to the efficacy of SSRIs in treating the depression seen in some patients with diabetic foot pain, as well as to the efficacy of the tricyclics for pain and depression [88]. Sacerdote et al. also implicated serotonin and other neurotransmitters and neurohormones in the analgesic effects of tricyclic antidepressants [89].

Serotonin has been most written about as a promoter of REM sleep. Studies with p-chlorophenylalanine (PCPA) have demonstrated symptoms of non-restorative sleep, pain, and somatic and neurovegetative signs of depression as a result of 5-HT depletion. Symptoms that surfaced in human work with PCPA include tiredness, dizziness, nausea, headache, and constipation [90]. Silberstein has described a link between 5-HT and migraine, while viewing 5-HT as a modulator of overall sensory responsiveness with less involvement in specific sensory experiences [91].

More recent formulations of 5-HT's role in sleep parallel Silberstein's view of 5-HT's role in the sensory realm. Serotonin is seen to play a modulatory function in sleep, in which 5-HT is involved with both wakefulness and sleep induction through actions at different receptors and in different brain regions, and through interactions with other neurotransmitters [82].

Other neurotransmitters, such as acetylcholine, have effects that may affect both pain and sleep, providing a neurobiological scaffolding for comorbid pain and sleep problems. Cholinergic systems in the brain also have critical modulatory roles in attention, alertness, consciousness, and cognition via prominent pathways in basal forebrain and rostral brainstem. Pedunculopontine cholinergic neurons modulate REM sleep [92]. Animal data have indicated local brain microinjection of the cholinergic agonist carbechol can induce antinociception [93].

The hypothalamic-pituitary-adrenal cortex (HPAC) arm of the stress- response axis will be activated with pain and affects sleep. Vgontzas et al. reported positive correlations of percent REM sleep and the HPAC-axis components epinephrine, urinary free cortisol, dihydrosyphenylglycol and dihydroxyphenylacetic acid in healthy human subjects [94].

Another important neurochemical system is the endogenous opioid peptides, clearly involved in the descending modulation of pain and also interacting with other neurotransmitter systems important in pain control [95]. Reinoso-Barbero and Andres [96] reported animal data in which microinjections of opioid into the nucleus of the solitary tract (NST) enhanced slow-wave sleep. The NST is speculated to have a role in the sleep cycle; it also contains the highest concentration of opioid receptors in the medulla.

Neuroimmune interactions may also be involved in comorbid pain and sleep problems. Painful infectious or inflammatory illness may affect sleep through the actions of excitatory cytokines such as interleukin-1 and tumor necrosis factor. These may act on sleep through complex interactions with other neurotransmitters and neurohormones [97]. Infectious challenges, via cytokines, affect REM and non-REM sleep [98].

Excitatory amino acid (EAA) neurotransmitters (eg, glutamate) are major effectors in peripheral and central sensitization with nerve injury. As such, they are important in the neurobiology of neuropathic pain. They also appear to be important in sleep regulation. Recent data suggest that EAAs play a central role in transducing light information to the suprachiasmatic nuclei (SCN) [99]. The hypothalamic SCN are critical generators of various circadian rhythms, including body temperature and sleep cycles in mammals [100]. EAA receptors and receptor subunits, as well as mRNA encoding for a glutamate transporter protein, have been identified in the suprachiasmatic nucleus (SCN) [101]. In addition to mRNA linked to the EAA system, other changes in gene transcription during sleep deprivation and extended wakefulness have been summarized by Toppila and Porkka-Heiskanen [102].

Beyond the various endogenous neurochemical and neurohormonal factors discussed, sleep is affected by various exogenous factors, including learning, habituated sleep behavior and learning, food intake, sleep deprivation, exercise, and various other exogenous factors that will be reviewed in the next section. Garcia-Garcia and Drucker-Colin [103] argue that these exogenous factors and the complexity of the endogenous neurobiology confound precise delineation of the pathophysiology of sleep problems [103]. This intricate interplay of factors is further complicated by considerable individual variation in levels of the involved neurochemicals found in healthy men [104].

The neurobiology of sleep disturbance in chronic pain has overlap with the neurobiology of depression and sleep. The current state of knowledge suggests interventions aimed at pain control or depression may also benefit sleep. For example, prescribing dextromethorphan to augment opioid analgesia or gabapentin to reduce neuropathic pain, each decreases EAA activity. They will therefore very likely also improve sleep via their EAA effects. Treatment of infection and inflammation may af-

fect the sleep-wake cycle through effects on cytokines. Serotonergic antidepressants (eg, tricyclics and newer serotonergic agents such as mirtazapine and nefazadone) may help with sleep through modulation of 5-HT. Conversely, anticholinergic side effects of various medications may impair alertness and cognition, worsening fatigue and functional impairment from poor sleep.

We present some current suspected neurobiological intersections of pain, sleep, and mood, preliminary and speculative as they are, in hopes that clinicians will be more sensitive to possible multiple effects of prescribed medications. In presenting the highly individual and exogenous issues that are at work in sleep regulation, we hope to caution unrealistic expectations of pharmacotherapies alone.

Treatment Approaches

Pharmacologic

Traditional benzodiazepines and barbiturates are known to promote sleep and drowsiness, and are often prescribed for complaints of insomnia. Although their use for long-term treatment of insomnia has been discouraged [105,106], epidemiological studies throughout North America show that patients with insomnia report sedative-hypnotic use ranging from 2.2% to 15.0% [1,107,108].

The prevalence of sedative-hypnotic use among individuals with chronic pain and sleep disturbance may exceed that of insomniacs in the general population. In a survey of 127 consecutive rheumatic patients, 29% reported benzodiazepine use for a mean duration of 4.1 years, and 78% of these individuals took the medication for insomnia related to pain [109]. In another survey of 114 general chronic pain patients, 38% reported benzodiazepine use, 60% of whom reported taking the medication for over one year. Forty-four percent (44%) used a benzodiazepine solely for sleep disturbance, while 42% used the medication for sleep and other reasons such as anxiety, muscle relaxation, and pain [110].

The efficacy of sedative-hypnotics for individuals with chronic pain conditions has been questioned. Of particular importance is the finding that hypnotics decrease stages 1, 3, 4, and REM of sleep, while increasing stage 2 sleep [111]. Although benzodiazepines have been shown to decrease sleep latency, decrease awakenings, and increase total sleep time [111], Hardo et al. [112] found that arthritic individuals who received sedative-hypnotics at night reported significantly higher levels of pain and greater disability than those who were not receiving sedation.

In an outpatient setting, King and Strain [110] found that benzodiazepines did not significantly improve sleep for individuals with chronic pain conditions when compared to individuals with chronic pain who did not use these medications. Recent indirect evidence suggests that benzodiazepines may antagonize opioid analgesia. In a double-blind, placebo-controlled study of 71 surgery patients, the benzodiazepine antagonist flumazenil was found to enhance morphine analgesia [113]. Further study is needed to determine whether sedative-hypnotics affect the efficacy of opioids prescribed for some patients with nonmalignant pain conditions.

Some evidence suggests that newer hypnotic agents are more effective and safer than older sedative-hypnotics. Medications with greater half-lives are more likely to be associated with daytime somnolence, as are higher doses. However, a variety of medications with intermediate and short half-lives are available and may have fewer adverse side effects than the older compounds [114]. Additionally, nonbenzodiazepine compounds, such as zolpidem and zaleplon have the potential for fewer daytime side effects. In a double-blind, placebo-controlled crossover study of 3 doses of zolpidem, Moldofsky et al. [115] found that 16 fibromyalgia patients reported increased total sleep time, fewer awakenings, reduced sleep onset latency, and increased daytime energy. No effects on pain or mood were noted in this study. In the author's clinical experience, short-acting medications such as zaleplon may be associated with frequent awakenings. Further data and experience may show that in some chronic pain conditions, in which there is regular input to the reticular activating system from the medial spinothalamic tract, short half-life sedative hypnotics many not be effective. Chronic pain patients have sleep disturbances, which appear different from more common psychophysiologic insomnia in pain-free patients. Atypical antipsychotics can be used in pain patients with refractory initial and terminal insomnia who failed nonbenzodiazepine hypnotics. Clonazepam may be helpful in some of these patients, due to its longer half-life. Clonazepam also has sustained anticonvulsant properties, its anticonvulsant action forming the basis of its FDA registration, and may decrease neuropathic pain, as suggested in reports on oral and phantom limb pains [116,117]. Other benzodiazepines have shown little analgesic promise [118].

Low-dose tricyclic antidepressants are commonly prescribed for the treatment of certain chronic pain disorders, particularly nerve injury or neuropathic

pains [88]. These medications have sedating antihistaminic and anticholinergic side effects that some patients find helpful for sleep, although only a few studies document their efficacy in sleep. The relevance of tricyclics' REM-suppressing action, helpful in depression, is not known in chronic pain. There appears to be a clear tricyclic sleep benefit in depressed pain patients, and nondepressed individuals with neuropathic pain also appear to sleep better. In the latter case, sleep improvement may be secondary to pain reduction.

Some data suggests chronic pain patients report a positive effect on sleep with 75-mg doses of amitriptyline compared to placebo [119] and when compared to lower doses (25-mg and 50-mg) [120]. However, higher doses are also associated with increased side effects, including dry mouth and drowsiness during the day [120]. In addition, tricyclic antidepressants may contribute to nocturnal myoclonus [111]. Newer sedating antidepressants such as trazadone, mirtazapine, and nefazadone have unproven effects on sleep in the pain context. These newer compounds hold promise, and have been successfully used in depressed pain patients. They appear to avoid the sleep disturbances seen with SSRIs, which have a stimulating, agitating effect through specific postsynaptic 5-HT receptors. Some patients may develop a cumulative sleep deficit when treated with the most commonly prescribed SSRIs (eg, fluoxetine, sertraline) [121]. Fortunately SSRIs are not in use in the majority of cited studies examining sleep disturbance in pain patients, since this could represent a significant confound.

Several other medications have been tested for the treatment of pain and sleep, however success has been limited. Chlormezanone, a muscle relaxant reported to have some benzodiazepine-like effects, was found to have no therapeutic benefits for patients with fibromyalgia in a double-blind placebo-controlled study [122]. Zopiclone, a nonbenzodiazepine hypnotic not available in the United States, has been shown to increase delta sleep, when tested in a double-blind randomized placebo-controlled study with persons with fibromyalgia (N = 41). Results revealed a significant amount of improvement in daytime tiredness and subjective sleep complaints but no change in sleep structure on polysomnography. In addition, zopiclone had no effect on pain or morning stiffness [123]. Unfortunately, a great deal of reported treatment data relates to the controversial fibromyalgia syndrome, and these data are not easily generalized to other patient populations.

Treatment of primary sleep disorders that coexist with chronic pain conditions requires careful thought and consideration. As discussed earlier, resolution of sleep disorders with specific treatments can significantly improve the quality of sleep for individuals with chronic pain (eg, continuous positive airway pressure (CPAP), mouth appliance, decreased alcohol intake, and weight loss in sleep apnea). The use of hypnotic agents and opioid analgesics in undiagnosed sleep apnea can result in an increase in the frequency and severity of episodes of apnea, especially in older adults [106]. Restless legs syndrome (RLS), a condition specifically identified in some of the cited studies of chronic pain and sleep disturbance, has been treated with various pharmacologic agents, including adrenergic blocking agents, levodopa/carbidopa combinations, and benzodiazepines [124]. Wagner et al. [125] performed a randomized, double-blind, placebo-controlled study of RLS using clonidine, an adrenergic blocking agent that has been used for persons with chronic pain, especially sympathetically maintained neuropathic pain. Subjectively, clonidine relieved leg symptoms and morning drowsiness. Objectively, clonidine decreased sleep latency but had the adverse effects of increased REM latency and decreased time in REM sleep. Patients showed no improvement in total sleep time, sleep efficiency, number of arousals, or number of limb movements during sleep. Patients did, however, show a trend towards more stage 3 and 4 sleep [125]. Montplasir et al. found that the majority of physicians specializing in sleep disorders recommend benzodiazepines for mild cases of restless legs syndrome or periodic limb movements in sleep [126]. Questions remain about the use of these medications in patients with chronic pain and restless legs syndrome or periodic leg movements. Therefore, long-term use of benzodiazepines for these co-occurring sleep disorders should be made cautiously, with careful monitoring of the effects.

The use of hypnotics for the treatment of sleep disorders generally, and in patients with chronic pain conditions, has been controversial. Although hypnotics do promote sleep induction and maintenance, many researchers and clinicians argue that these benefits are short-lived. In addition, benefits may be outweighed by problems such as cognitive and psychomotor impairment, possible dependence, and changes in polysomnographic changes in stage 3 and stage 4 sleep [110–112]. However, newer hypnotic agents may mitigate some of the perceived adverse effects of benzodiazepines, and clonazepam may have anti-neuropathic analgesic effects. Tricyclic antidepressants, new sedating antidepressants, and atypical antipsychotics may also be useful in

promoting sleep improvements in pain patients. Of course, identified specific sleep disorders (eg, sleep apnea, restless legs syndrome) must be directly treated. Finally, the best possible pain control will enhance sleep.

Non-pharmacologic

Nonpharmacologic treatments designed to reduce sleep disturbance and chronic pain have been used as an adjunct to pharmacologic treatment or to avoid side effects, tolerance, and drug interactions of pharmacologic therapy. Non-pharmacologic treatments include behavior modification, relaxation, cognitive-behavioral interventions, exercise, and phototherapy [127]. Three very common behavior modification strategies are *sleep hygiene*, *stimulus control*, and *sleep restriction*. *Sleep hygiene* involves tracking and changing behaviors that contribute to insomnia, such as over-stimulation before sleep and the use of alcohol, tobacco, and caffeine [128]. *Stimulus control* refers to changing conditioned associations that contribute to insomnia, such as limiting activities in bed to sleep and sex. *Sleep restriction* refers to restricting the hours a patient sleeps to the number of hours he/she is currently sleeping. Sleep deprivation generally follows, and sleep time can be systematically increased in the non-pain patient [129].

Empirical evidence validates the effectiveness of nonpharmacologic strategies for the reduction of insomnia. Morin et al. [128] performed a meta-analysis that involved 59 treatment outcome studies for the management of insomnia that included 2,102 patients. Psychological interventions averaging 5 hours of therapy time produced results in decreasing sleep latency and increasing sleep maintenance when compared to untreated controls. Stimulus control and sleep restriction were found to be the most effective strategies and were far superior to sleep hygiene education alone [128]. Decreases in sleep onset latency, following treatment with stimulus control and sleep restriction techniques, have been documented by polysomnography and daily diaries in a small number of patients [129]. Structured sleep hygiene with light treatment was found to be superior to sleep hygiene instructions alone, and to sleep hygiene with late afternoon moderate exercise, in a study of 30 persons with psychophysiologic insomnia [130].

In 1996, the NIH Technology Assessment Conference [131] heard expert presentations over 1 1/2 days and reviewed the current literature on the integration of behavioral and relaxation approaches in the treatment of chronic pain and insomnia. They found strong support for the use of relaxation techniques and moderate support for the use of cognitive-behavioral strategies and biofeedback in reducing chronic pain. Evidence for the use of relaxation and biofeedback to improve sleep was found, but the magnitude of clinical improvement in sleep onset and total sleep time, by these methods alone, was questioned by the panel.

Exercise has also been hypothesized to improve sleep quality for individuals with chronic pain conditions. In a small pilot study in 1976, Moldofsky and Scarisbrick were unable to induce musculoskeletal symptoms in long-distance runners using selective stage 4 sleep disruption. In contrast, sedentary individuals developed musculoskeletal symptoms which mimicked fibrositis [73] Individuals who are physically fit have been shown to have more slow wave sleep than unfit individuals [132].

It is also possible that improved aerobic fitness may decrease pain that could in turn improve sleep. Fibrositis patients who trained aerobically for 20 weeks experienced reduced pain as compared to a group who received only flexibility training. The authors postulated that exercise may affect pain sensitivity by activating the body's endogenous opioid system, and may confer other benefits by improving mental status and increasing slow wave sleep [133]. Other nonpharmacologic interventions have been proposed to increase sleep. For example, Hart et al. noted that modification of local factors (shielding pressure points, earplugs, and eyeshields) might improve the sleep of chronic pain patients [20].

Overall, the literature on nonpharmacologic approaches to improving sleep shows that these approaches can affect the overall quality of sleep. Sleep restriction ideas and stimulus control suggestions can be easily disseminated by pain physicians. Suggesting sleep restriction, in particular, may help patients reduce the worry associated with not receiving enough sleep. A directive to schedule the amount of sleep received to the current amount and gradually increase it is a "low tech" suggestion that may yield improvement. However, some individuals will likely need individualized schedules that would be provided by a behavioral medicine specialist. Encouragement to participate in some type of exercise can also be helpful in improving sleep.

Conclusion

Sleep disturbance is a common clinical complaint for individuals with chronic pain conditions including musculoskeletal pain, rheumatic diseases, headache, and fibromyalgia. The prevalence of sleep disturbance appears to be greater for persons with

chronic pain conditions than for individuals in the general population, although widespread epidemiological studies have not yet been conducted. The types of sleep disturbance most often reported by persons with chronic pain conditions are insomnia, daytime sleepiness, and nocturnal awakenings. In addition to general sleep complaints like insomnia, it appears that some patients have comorbid primary sleep disorders such as sleep apnea, restless legs syndrome, or periodic movements in sleep.

Studies that document self-reported sleep disturbances by polysomnography are infrequent in the literature and mostly concentrated on small samples of patients with fibromyalgia. These studies have shown increased sleep fragmentation and nocturnal movements, and decreased slow wave sleep and sleep efficiency for persons with chronic pain, when compared to individuals without pain conditions. Differences in stages of sleep have been noted for individuals with different types of headache. Finally, polysomnography has documented the presence of sleep disorders, most notably sleep apnea and periodic limb movements that may contribute to decreased sleep efficiency. Objective evidence to document sleep disturbances and the presence of sleep disorders is significantly lacking in the literature. Further studies are needed to investigate mechanisms and types of sleep disturbance that may be treated independently and concurrently with pain. However, the presence of sleep disturbance indicates that patients should be carefully screened to rule out primary sleep disorders.

Associated clinical features, such as depression, anxiety, and fatigue may complicate the diagnosis and treatment of sleep disturbances for persons with pain conditions. Sleep disturbance is a symptom of several mood disorders (eg, depression, anxiety) that often coexist with chronic pain. Causal models proposed thus far have been insufficient to answer the question, "Which comes first?" with respect to pain and sleep disturbance, and few have speculated on the specific relationships between sleep, pain, and mood. One of the few longitudinal studies that addresses the relationships between mood, pain, and sleep disturbance found that pain at the baseline period was predictive of sleep disturbance and that, over time, both pain and sleep disturbance were predictive of depression [19]. However, standardized measures of sleep were not used in this study.

Research related to the mechanisms of sleep disturbance in persons with chronic pain conditions is also limited. Although pain and discomfort undoubtedly make sleep difficult, some evidence suggests that the relationship is far more complex than originally believed. One possible hypothesis is the intrusion of alpha-delta sleep patterns, as shown on polysomnography. This pattern, found in fibromyalgia and possibly in other disorders, may contribute to a cycle of nonrestorative sleep and musculoskeletal pain. There is some evidence to support the hypothesis that slow wave sleep deprivation induces musculoskeletal pain. However, study samples are small, and the results of these experiments have not always been replicated. There is a need for additional studies on alpha-delta sleep in other pain populations. There is also some evidence that neurobiological links exist between pain and sleep involving such neurochemicals as serotonin, norepinephrine, acetylcholine, and endorphins, which may be involved in regulation of pain, sleep, and affect. This complex area of pathophysiologic linkage is currently more speculative and theoretical than evidence-based.

One difficulty with studies about sleep disturbance is the lack of utilization of standardized measures. Individuals are sometimes self-classified as "good" and "poor" sleepers, a distinction that is probably adequate for some purposes, but not adequate for systematic study of the types of sleep disturbance and the level of disability they may cause. Polysomnography, along with standardized questionnaires, diary methods, and actigraphy are all measures of sleep disturbance that can provide more detailed information than whether a person is a "good" or "poor" sleeper, and should be used in future studies.

Treatment of sleep disturbance has been primarily with medications in the past, although nonpharmacologic methods of pain control and sleep restoration have been available for some time. Medication treatment decisions are frequently complicated by the need to decide how to balance medications for pain and sleep disturbance. At least in a significant number of chronic pain patients, aggressive pain treatment appears to be the appropriate initial focus of treatment, because in many patients sleep and mood disturbances develop after the onset of the pain condition, and are associated with pain intensity. Many practitioners opt for low-dose tricyclic antidepressants, although few studies have tracked their specific effect on sleep architecture, or strongly support clinical efficacy. Non-pharmacologic interventions have shown efficacy in improving sleep. Physicians or other health professionals can easily administer some nonpharmacologic interventions (eg, suggestions for better sleep hygiene); behavioral medicine specialists should deliver other interventions (eg, biofeedback or behavioral modification) requiring a more intensive approach to institute behavior change.

Accurate diagnosis of the etiology of sleep disturbance is critical in order to determine the proper treatment. Questions about the patient's specific sleep disturbance, and whether the sleep disturbance existed prior to the onset of the pain condition, will help the practitioner evaluate whether the patient may have a sleep disorder, and the nature of the current sleep disturbance. Treatment should be carefully selected and revised based on ongoing evaluation of specific sleep difficulties. Further studies of the pathophysiology, prevalence and treatment of sleep disorders are critical to address this important clinical concern.

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