Pain and Sleep in Medical Diseases: Interactions and Treatment Possibilities

A Review

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Epidemiological and clinical studies have given support for a strong association between pain and sleep disturbances. The present article reviews the present literature on pain and sleep in different patient groups with focus on studies based on objective sleep measurements. In most studies of pain patients, different sleep disturbances with alterations in sleep structure and discrete electroencephalography (EEG) abnormalities, such as alpha-EEG anomaly, were seen. A majority of studies have included patients with musculoskeletal disorders, but also in other pain patients, sleep fragmentation and disturbances of sleep microstructure may aggravate the pain and contribute to the daytime symptoms. Experimental studies in healthy subjects have given support to the hypothesis based on the clinical findings, and it is hypothesized that increased sleep depth may facilitate the sleep continuity in pain patients. Although changes in sleep structure are frequent in pain patients, the importance in the individual patient is yet unknown. Thus, in the clinic, sleep recordings are only recommended in selected patients with severe complaints of disturbed sleep and/or related daytime complaints. Several analgesics have the potential to alter the sleep structure and this may limit the use of these drugs in pain patients. Most studies were, however, performed in healthy individuals and the long-term effect of analgesics on sleep structure should be evaluated in patients with chronic pain. Short-term use of hypnotics may be of some value in selected patients as they can improve sleep satisfaction and increase daytime energy. Pain, however, is probably only affected to a minor degree by these drugs and additional treatment must frequently be recommended. Future studies are highly recommended in this area and should rely on controlled, objective experiments where polysomnography is performed together with signal analysis of the EEG microstructure.

CURRENT CLAIM: Interactions between sleep and pain are important in medical illness and shall be considered in the treatment of these patients.

For decades physicians have intuitively been aware of the relationship between the homeostatic functions of sleep, well-being, and pain (Moldofsky, 1993; Drewes, 1999). Pain has been reported as a leading cause of insomnia in medical illness, where more than 70% of the patients complain of sleep problems (Wooten, 1994; Drewes et al., 1994) and in studies of patients with non-specific pain, a high prevalence of subjective sleep disturbances have been reported (Pilowsky et al., 1985; Magni et al., 1994). Also, in experiments where polysomnography was performed, sleep disturbances were found in patients with pain due to different diseases (Drewes, 1999). Most studies of pain and sleep, however, have focused on musculoskeletal diseases where the prevalence of sleep disturbances has been reported to be very high (Wolfe et al., 1990; Drewes et al., 1994).

The belief that sleep is a static condition has been replaced by the assumption that this state is a dynamic form of rest that conserves energy and permits reorganization of cortical neuronal activity among other functions. Especially the deepest sleep stages seem to reflect homeostatic processes for the body and the mind, although this theory cannot explain all aspects of mammalian sleep (Horne, 1988). In accordance with sleep as a restorative process, anabolic hormones are released mainly during sleep and evidence exists that a boosting of the immune system occurs during the night (Moldofsky, 1995). Thus, there seems to be a relationship between dynamic changes in sleep and various cellular, hormonal and immunological functions. Pain and other components in the disease may influence the sleep process and alter these essential parameters, thereby interacting with the disease process. Correspondingly, many of the daytime symptoms in rheumatic patients such as pain, stiffness and fatigue may have a close link to the non-restorative sleep pattern associated with the disease (Moldofsky, 1993). Knowledge of the abnormalities in sleep may therefore improve our understanding of the disease and lead to a better treatment of the patients.

Pain is the net effect of peripheral nociceptive activation and different biochemical, physiologic and psychologic mechanisms that involve different parts of the central nervous system depending on the nature of the disease. Therefore, pain is an individual experience. Such differences in pain must be considered when sleep disturbances and other phenomena accompanying medical illness are studied. It is probable that the interactions between sleep and pain are very heterogeneous depending on the individual person and/or disease.

Epidemiologic Studies of Pain and Sleep

Epidemiologic studies have shown a high prevalence of sleep problems in patients with medical illness, and in many
diseases pain may be the leading cause of insomnia (Currie, 1993; Wooten, 1994; Drewes et al., 1994). Correspondingly, in a survey of 4,064 Swedish men, Gislason and Almquist (1987) found an increased prevalence of sleep problems among patients with somatic diseases, especially those with pain due to rheumatic complaints in comparison with healthy subjects. In a community health survey of 1,765 subjects, Moffitt et al. (1991) found that pain was the variable most strongly connected to sleep problems, and arthritis was the factor most significantly contributing to pain. In many patients with poor sleep the psychological problems may be a major cause of the complaints, and it shall not be underestimated that psychological factors may contribute to the sleep disturbances in somatic diseases (Phillips and Cousins, 1986).

Sleep disturbances were most extensively studied in patients with rheumatic disorders. Approximately 75% of patients with fibromyalgia and 60% of patients with rheumatoid arthritis reported sleep difficulties (Drewes, 1999). Thus, in a study of patients with fibromyalgia and rheumatoid arthritis, related daytime symptoms such as fatigue and morning stiffness were present in most of the patients, and the prevalence of nearly all sleep-related problems was reported significantly higher in the two patient groups in comparison with controls (Drewes et al., 1994).

Sleep Disorders in Patients with Pain—Objective Findings

Sleep disorders have been reported in most patients with pain as a major complaint—for review see Wooten (1994). Sleep is most easily measured by means of questionnaires. Such studies have also been performed in patients with pain and sleep disorders (Crosby, 1991; Drewes et al., 1994; Martinez et al., 1995). Although questionnaires may give important information regarding sleep habits, severe limitations exist. Some previous studies have found a reasonable correlation between subjective assessments and more objective (i.e., polysomnographic) findings, but in others it was apparent that the subjective sleep quality scale was not an indicator of the objective state (Drewes, 1999; Currie, 1993). Finally, it should be emphasized that sleep dissatisfaction is very frequent in the general population as well (Partinen et al., 1983). Thus, polysomnography or similar measurements are necessary if the quality and quantity of the sleep disturbances shall be estimated. Moreover, prominent trends in EEG power density across the night may clearly be disregarded if analysis of sleep is based exclusively on conventional scoring procedures and obviously there is a need for a more dynamic model in the description of the sleep-wake continuum. Thus, signal analysis may unmask discrete EEG "microstructure" abnormalities, which is not seen in the visual scoring (Hasan, 1985; Armitage et al., 1992; Pardey et al., 1996). Objective monitoring of sleep was, however, only performed in selected patients (Table 1). In most studies of patients with pain, sleep disturbances with fragmented sleep and a decrease in sleep efficiency and slow wave sleep (SWS) was seen. Moreover, several studies have shown sleep microstructure abnormalities. The following review will focus

### Table 1

**Selected Findings in Sleep Studies of Different Pain-Related Diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>N</th>
<th>Main Objective Sleep Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific Chronic Pain</td>
<td>17</td>
<td>Fragmented sleep, increased number of arousals.</td>
</tr>
<tr>
<td>Ischemic Coronary Heart Disease</td>
<td>84</td>
<td>Decrease in SE and SWS. Correlation between severity of disease and sleep disturbances.</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>12</td>
<td>Increased NREM 1 and low SE in the first days followed by increase in SWS.</td>
</tr>
<tr>
<td>Headache</td>
<td>79</td>
<td>Different sleep disorders dependent on the type of headache.</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>10</td>
<td>Low SE and REM sleep.</td>
</tr>
<tr>
<td>Peptic Ulcer Disease</td>
<td>10</td>
<td>Fragmented sleep and increased sleep latency.</td>
</tr>
<tr>
<td>Irritable Bowel Syndrome</td>
<td>18</td>
<td>REM sleep abnormalities.</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>11</td>
<td>Motor activity (and reflux) sleep stage dependent.</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>206</td>
<td>Disturbances in sleep architecture with more superficial and fragmented sleep. Apneas and PLMS during sleep. Disturbed sleep microstructure with increased alpha-EEG and less power in the lower frequencies.</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>134</td>
<td>Abnormal sleep physiology with fragmented sleep and increase in primary sleep disorders. Increased alpha-EEG, PLMS. Correlation between daytime symptoms and selected sleep variables.</td>
</tr>
<tr>
<td>Primary Sjögrens Syndrome</td>
<td>10</td>
<td>Decreased SE and increased wakefulness.</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>29</td>
<td>Increase in NREM 1, more body movements, alpha-EEG pattern.</td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>11</td>
<td>NREM 1, movement time and SWS associated with pain complaints.</td>
</tr>
<tr>
<td>Low Back Pain</td>
<td>30</td>
<td>Low SE and disturbed sleep architecture. Decreased SWS and evidence for sleep microstructure disturbances.</td>
</tr>
</tbody>
</table>

Only experiments with objective sleep staging and comparison with healthy controls are included. For details and references, see text. N=number of patients; SE=Sleep efficiency; SWS=slow wave sleep; PLMS=periodic movements of the legs during sleep; alpha-EEG=8-12 Hz EEG activity overriding the normal EEG pattern in NREM sleep Stages 2-4.
on selected diseases, where the studies were mainly based on polysomnographic recordings.

Coronary Heart Diseases

The relation between pain and sleep was investigated in several studies in patients with coronary heart disease. Karacan et al. (1969) found a decrease in SWS and sleep efficiency in patients with angina pectoris and similar findings were reported by Cassano et al. (1981), who suggested a chronobiological factor in the distribution of the pain. Murao et al. (1972) found that ischemic episodes most frequently occurred during rapid-eye-movement (REM) sleep and Dohno et al. (1979) found evidence of fragmented sleep in patients with coronary heart disease, and more awakenings and sleep stage changes in those who were most seriously ill. Broughton and Baron (1978) investigated the sleep pattern in patients for up to 13 days after acute myocardial infarction. High amounts of wakefulness and time spent in non-rapid-eye-movement (NREM) sleep was found. Stage 1 and poor sleep efficiency were seen in the first days after the attack, but SWS increased and remained high until nine days after the infarction. It must therefore be concluded that severe sleep disturbances may influence the well-being in these patients.

Neurological Diseases

Several authors have reported sleep disturbances in patients with pain due to neurological diseases. Thus, pain due to peripheral neuropathies, carpal tunnel syndrome and multiple sclerosis was reported to interfere with sleep (Page and Chen 1997; Lehtinen et al., 1996; Tachibana et al., 1994). Sleep dissatisfaction was also reported in patients with headache, but only a few studies were based on objective recordings. Drake et al. (1990) recorded sleep in patients having either migraine, tension headache or mixed-element headache. Whereas patients with migraine had nearly normal sleep structure, the other two groups experienced more sleep disturbances with decreased sleep efficiency and SWS as well as an increase in the number of awakenings. Sleep walking and headache are frequently associated and Paiva et al. (1997) found specific sleep disorders in 55% of patients with onset of headache during the nocturnal sleep period (9% of all headache complaints). Treatment of the sleep disorders resulted in improvement or absence of the headache in all subjects.

Visceral Diseases

In duodenal ulcer disease the pain is typically worst at night when the acid production is high, and in a study by Nakazawa et al. (1982) the sleep in patients with peptic ulcer was fragmented with increased latency to sleep stages. Complaints of pain and sleep disturbances are also reported in patients with irritable bowel syndrome and more studies found evidence for REM sleep abnormalities and more high frequency EEG activity in these patients (Kumar et al., 1992; Orr et al., 1997). In esophagitis an increase in reflux events has been observed during the night (Orr, 1994) and esophageal motor activity was found to be sleep stage dependent (Castiglione et al., 1993). Thus, nightly interactions between enteric motor function and sleep may be important in the understanding of the symptoms in patients with gastroenterological diseases. In women with dysmenorrhea, Baker et al. (1999) demonstrated decreased sleep efficiency and REM sleep compared with pain-free phases of the menstrual cycle (and healthy controls). It was concluded that the dysmenorrheic pain might exacerbate daytime symptoms due to the effects on sleep structure.

Rheumatic Diseases: Sleep Macrostructure

As seen in Table 1, patients with musculoskeletal diseases were most extensively investigated among patients with pain. Sleep disturbances were seen in patients with primary Sjögren’s Syndrome, osteoarthritis, anklyosing spondylitis, and low back pain, among others (Gudbjörnsson et al., 1993; Moldofsky et al., 1987; Leigh et al., 1988a, 1988b; Jamieson et al., 1995; Atkinson et al., 1988; Staedt et al., 1993; Mahowald and Mahowald, 2000a). In these patients a decrease in sleep efficiency was seen with much time spent in wakefulness during the night. The sleep was typically more superficial and fragmented, and some studies showed a high incidence of primary sleep disorders such as periodic leg movements during sleep (PLMS) and sleep apnea. Most studies were performed in patients with fibromyalgia and rheumatoid arthritis. In fibromyalgia most studies have shown a tendency towards a more superficial sleep macrostructure. Apneas and PLMS may contribute to sleep fragmentation and daytime symptoms, but only in selected patients as these primary sleep disorders were only found in few studies—for review see Drewes (1999). Sleep disturbances are also frequent in rheumatoid arthritis with fragmented sleep and an increase in primary sleep disorders (Moldofsky et al., 1983; Mahowald et al., 1989; Lavie et al., 1991; Hirsch et al., 1994; Drewes et al., 1998a). The most consistent abnormality was PLMS with variable severity in many patients, whereas the different studies showed conflicting results regarding other sleep abnormalities. The importance of PLMS as a distinct syndrome has, however, been questioned. Severe PLMS may be asymptomatic (Montplaisir et al., 1994), and only when it is associated with evidence of arousal should it be considered as a probable reason for the sleep problems.

Rheumatic Diseases: Sleep Microstructure

Sleep microstructure disturbances (e.g., discrete EEG phenomena) were reported in some patient groups—such as in subjects with low back pain—where clusters of arousal were prevalent (Staedt et al., 1993). Sleep microstructure abnormalities may, however, be more important in fibromyalgia. Most papers have found that the alpha-EEG sleep anomaly is a consistent feature in these patients. This is most commonly defined as an excess of alpha (8-12 Hz) EEG activity overriding the normal EEG pattern in sleep stages NREM 2-4. Although some studies have shown a positive relationship between the amount of alpha activity and the severity of the symptoms in fibromyalgia, the presence of excess alpha-EEG in other patient groups and healthy subjects suggests that not all aspects of non-restorative sleep can be attributed to this anomaly (Pivik and Harman, 1995;
Mahowald and Mahowald, 2000b). Whether the alpha-EEG anomaly represents 1) a primarily central arousal mechanism, 2) a sleep maintaining process showing enhanced response in some diseases, or 3) reflects peripheral nociceptive stimuli, is still a matter of debate and possibly several mechanisms may play a role in the generation of this phenomenon in clinical settings (Drewes, 1999). Other frequency components may be important in the study of sleep microstructure, and in studies of Drewes et al. (1995a, 1995b) it was found that the power in the lower frequencies of the sleep EEG was decreased in patients with fibromyalgia with an abnormal decline during the night. According to the two-process model for sleep regulation proposed by Borbély et al. (1981, 1982), the EEG power in the low frequency range may be an indicator of the sleep process. The findings could therefore reflect disturbances of the normal homeostatic processes during sleep and partly explain the daytime symptoms in these patients.

In rheumatoid arthritis and other rheumatic diseases many studies have reported an increase in alpha-EEG during sleep. Sleep microstructure disturbances are however, not as pronounced as in fibromyalgia, and the role of discrete EEG alterations in other rheumatic diseases remains to be investigated in more detail—for review see Drewes (1999) and Mahowald and Mahowald (2000a).

Other Painful Diseases

Currie (1993) compared the sleep and daytime activity in patients with chronic pain attending a management program. The patients had fragmented sleep with an increase in nocturnal movements and arousals, and pain accounted for most of the variance in sleeping behavior. Sleep disorders are common in the dental profession and several sleep disorders are related both to non-painful (e.g., bruxism and xerostomia) and painful diseases such as chronic orofacial pain (Lavigne et al., 1999). Pain and associated sleep disturbances are also frequent in cancer patients suffering from pain. Thus, in a recent study, Miaskowski and Lee (1999) found decreased sleep efficiency in patients with bone metastasis, and additional research in that area is warranted.

Experimental Studies in Healthy Subjects

Experimental studies have shown that sleep deprivation causes sleepiness, fatigue, negative mood and impaired intellectual functions (Bonnet, 1994). Moldofsky and Scarisbrick (1976) showed a correlation between NREM 4 sleep deprivation in healthy subjects and increased morning tenderness, musculoskeletal aching and unusual somatic fatigue—symptoms that subsided over the following recovery nights. It was concluded that the alpha-EEG induction together with a decrease in NREM 4 sleep was able to induce fibromyalgia-like symptoms in healthy subjects. In subsequent studies however, the pain following SWS deprivation could not always be reproduced (Walsh et al., 1994; Old et al., 1998; Drewes et al., 2000a), although Lentz et al. (1999) recently showed that SWS deprivation in middle-aged women resulted in a decrease in the musculoskeletal pain threshold. It is up to future studies to address these very important aspects.

Animal studies have supported the evidence of an interaction between pain stimuli and different sleep stages. Although sleep in animals cannot be directly compared with that in man, there is some similarity of the sleep processes. Carli et al. (1987) investigated the sleep EEG pattern after a formalin injection in cats, and an increase in sleep latency and a decrease in what corresponds to SWS and stage REM was found. Landis et al. (1988) examined the sleep in rats with adjuvant arthritis. Following induction of arthritis there was fragmented sleep with a decrease in the deepest sleep stages and loss of the diurnal variation in sleep and wakefulness.

As great heterogeneity in pain patients exists, the different results from clinical studies are difficult to interpret. Pain is a highly complex subjective perception, and experimental pain studies where the stimulus as well as the evoked response can be controlled may help to standardize sleep EEG findings during conditions that mimic clinical pain. Drewes et al. (1997) developed a model where healthy subjects were exposed to experimental muscle, joint and cutaneous pain stimuli. EEG alterations comparable to those seen in the patient groups were seen, thus confirming the importance of the different EEG phenomena as markers of pain in rheumatic diseases. In a recent experimental study, Lavigne et al. (2000) showed that the nociceptive processing was attenuated throughout sleep stages, and probably patients with increased deep sleep may suffer less from pain during the night. Breus et al. (2000) recently found that pain induced by eccentric muscle exercise resulted in increased REM sleep with a trend towards an increase in SWS. These studies support the theory that increased sleep depth may facilitate sleep continuity in pain patients (Drewes et al., 1998a, 2000b). The disease process itself, however, may give alterations in hormonal/immunological relations, cytokine production, etc. These factors may influence pain level, sleep structure and several other basic functions such as the activity level and psychological symptoms. Thus, the interactions between pain and sleep may be rather complex (Figure1).

In an attempt to study these interactions Drewes et al. (1998a) used a statistical model where no a priori assumptions on the distribution of data were necessary (in contrast to ordinary multivariate models) and complex relations between the variables could be detected. Among the many clinical, biochemical and somnographic variables initially selected for the model, only subjective pain rating and joint pain were associated with sleep structure. Thus, increased pain ratings resulted in more awakenings and increased time spent in (compensatory) SWS. In a recent follow-up study the results were replicated (Drewes et al., 2000b). In conclusion, we believe that the interactions between pain and sleep are of major impact for patients with medical diseases and although many factors may interplay in complex diseases, the pain/sleep relations are robust and relatively independent from other components in the disease.
Especially where pain is dominating, the treatment must often focus on the size of the problem, and physical activity may also be changed with the possibility to influence both sleep and pain perception. The interactions between pain and sleep are probably robust even when considering the many other factors which interplay in medical diseases.

Treatment of Sleep Disturbances in Patients with Pain

As sleep disturbances are frequent in medical diseases, especially where pain is dominating, the treatment must often focus on the nightly complaints. Although changes in sleep structure are frequent in pain patients, the importance for the individual patient is unknown and sleep recordings are only recommended in selected patients with severe complaints of disturbed sleep or related daytime symptoms such as severe tiredness and fatigue. Medication is most frequently prescribed against the pain. Obviously pain relief is a major treatment goal, but treatment of restless sleep has also been shown to enhance the quality of life in patients with chronic illness. The diurnal distribution of analgesics is unknown, but the consumption of hypnotics is probably high in patients with pain, and in rheumatic diseases 15-70% regularly took these drugs (Hardo et al., 1991, 1992; Drewes et al., 1994). In comparison with otherwise healthy controls where the consumption of hypnotics is 3-4.5% (Partinen et al., 1983; Drewes et al., 1994; Hench, 1996), this focuses on the size of the problem. In some cases, like gastroesophageal reflux disease, the treatment can be specifically directed against the disorder, and no further therapy is necessary. Whenever there is evidence for primary sleep disorders, relevant examination and treatment are strongly recommended. In most cases, however, only symptomatic therapy is available. In the following, a review of the different treatment alternatives for pain and sleep disturbances is given with focus on studies where polysomnographic measurements were used.

Non-pharmacological Treatment

Especially in rheumatic patients, local factors may be treated with a comfortable mattress and pillows for support. Behavioral approaches, such as relaxation training, biofeedback and cognitive therapy, may also have effect in some patients (Morin et al., 1989; Richmond et al., 1996). Finally, it should be stressed that ordinary sleep hygiene arrangements, such as an undisturbed room with pleasant humidity and temperature, may improve sleep sufficiently (Espie, 1993).

Pharmacological Treatment

Several drugs may disturb the sleep structure (Nicholson et al., 1994) and such adverse effects must be taken into account in patients receiving various medications. Problems with interaction between drugs given for pain and/or sleep disturbances may also be important in selected patients. In the following, the effect of drugs especially used for pain patients will be discussed together with studies where hypnotics are used.

Analgesics and Related Medication

For treatment of pain, simple analgesics are often prescribed. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are known to inhibit prostaglandin synthesis mainly in the central nervous system and therefore they may interact with, for example, body temperature and sleep/wake functions. The effect of aspirin on sleep is controversial. In one study aspirin reduced SWS in healthy subjects, although no effects were previously found in poor sleepers (Horne, 1980). Murphy et al. (1994) found an increased number of awakenings and time spent awake in healthy young subjects receiving aspirin, and similar findings were reported in an animal study (Landis et al., 1989). These results cannot however be interpolated to patients with chronic diseases using varying doses and long-term administration of the drug. Acetaminophen, also being a prostaglandin synthetase inhibitor, probably has differential effects on sleep. Murphy et al. (1994) found no alterations in sleep after administration to healthy subjects, but Landis et al. (1989) found a sleep promoting effect on sleep in rats with adjuvant-induced arthritis in comparison with sleep in healthy animals. As aspirin in this study also increased time spent awake in arthritic rats, it was concluded that acetaminophen may have a better effect than aspirin on sleep during pain. No final conclusions can be drawn from these studies however, and experiments in patients with different medical diseases are warranted.

NSAIDs have been more extensively studied, although only a few experiments have used polysomnographic measurements for sleep. Most studies were conducted in patients with rheumatoid arthritis. In most of these studies there was a subjective effect on pain, morning stiffness and sleep (Drewes, 1999). In animal studies, a reduction in SWS and REM was reported (Inoué, 1989), and in healthy subjects the same effects as those induced by aspirin were seen (Murphy et al., 1994). Lavie et al. (1990) used actigraphy to obtain an objective estimate of sleep in patients with rheumatoid arthritis. After treatment with two NSAIDs, no effects on sleep parameters...
were used in some studies, showing effect on subjective sleep. Chlorpromazine, which was otherwise shown to reduce pain in fibromyalgia (Jacobsen et al., 1991). In different rheumatic diseases, skeletal muscle relaxants with sedative properties were used in some studies, showing effect on subjective sleep assessment and pain, whereas in others no therapeutic effects were seen (Drewes, 1999). The differences can probably be attributed to various central actions of the compounds, but as no polysomnographic sleep measures were used, the results must be interpreted with caution. The major side effects also limit the use of these drugs. The same accounts for chlorpromazine, which was otherwise shown to reduce pain and increase delta sleep in patients with fibromyalgia (Moldofsky and Lue, 1980). Amitriptyline has been shown to improve sleep and decrease pain in 20-30% of patients with fibromyalgia and other patients with chronic pain disorders (Oghena and Van Houdenhove, 1992; Drewes, 1999). Carette et al. (1995) compared the clinical and recorded sleep parameters in 22 fibromyalgics after treatment with amitriptyline or placebo in a double-blind, cross-over trial. A clinical improvement was seen in 27% after amitriptyline treatment. Compared with baseline there was an increase in NREM 2 during active treatment. A decrease in delta activity was also evident, but otherwise no changes in sleep parameters were seen. Alpha-EEG sleep ratings decreased in only two of those patients whose clinical symptoms improved. Therefore, although amitriptyline can ameliorate clinical symptoms, the negative sleep profile may counteract this effect and give limitations in the use of the drug. The serotonin concentration in the central nervous system has been linked to sleep and perception of pain (Wilke and Mackenzie, 1985). Treatment with the serotonin precursor L-tryptophan in patients with fibromyalgia has given conflicting results. Moldofsky and Lue (1980) found no effect on pain or sleep pathology and correspondingly, treatment with a serotonin re-uptake inhibitor did not have any effects on the symptoms (Nørgaard et al., 1995). However, an Italian group showed improvement in all clinical variables when patients were treated with 5-hydroxy-L-tryptophan (Puttini and Caruso, 1992). Further controlled studies supported by polysomnography are thus needed to re-examine these findings.

Opioids, although potentially addictive, may be necessary to control pain in patients with chronic diseases. In animal studies, systemic opioids were shown to decrease SWS and REM, whereas morphine microinjections at different sites in the central nervous system produced a variety of effects on sleep stages, thus suggesting the importance of these substances in the regulation of sleep. In humans, parenteral morphine induced a decrease in SWS and REM, and an increase in wakefulness and NREM 1 together with an increase in alpha-EEG, among other findings (Reinoso-Barbero and Andrés, 1995; Drewes, 1999). Thus, morphine is supposed to give alterations which probably have negative effects on the homeostatic properties of sleep. No sleep studies using opioids in patients with pain have been conducted, however, and therefore no definitive conclusions can be drawn.

In conclusion, acetaminophen may not alter sleep structure in healthy subjects, whereas aspirin and NSAIDs probably have more negative effects in normals. In patients with medical diseases results may be different, and in rheumatoid arthritis NSAIDs do not seem to give objective sleep changes whereas the subjective feeling of sleep may improve. During amitriptyline and opioid treatment, a negative sleep profile may be induced, which can limit the use of these drugs in patients with pain. As pain patients are very heterogeneous, further studies are recommended to evaluate the sleep modulating effects of analgesics in different diseases.

Hypnotics and Related Drugs

As sleep problems are frequently reported in patients with pain, treatment with hypnotics may theoretically be of value. Furthermore, as sleep disturbances may theoretically have a negative impact on homeostatic aspects and lead to a decrease in the pain threshold, a pharmacological modulation of sleep continuity may be a therapeutic supplement, also with respect to daytime symptoms. Prescribing hypnotics for longer periods, however, may be harmful. Hardo and Kennedy (1991) investigated the consumption of hypnotics in patients attending the rheumatology clinic. Twenty-nine percent were regularly taking benzodiazepines and more patients in this group had complaints of severe pain. It was concluded that long-term treatment with benzodiazepines carries the risk of dependency with a possibility of severe side-effects, therefore restricted use was recommended. Several studies based on objective sleep recordings, however, have found a positive effect during treatment with hypnotics. Kavey and Altshuler (1983) found more total sleep time and fewer awakenings after the treatment of patients with flurazepam following herniorrhaphy. Therefore, the sleep promoting effect may be of benefit after minor surgery. In a study of osteoarthritic patients, Leigh et al. (1987) found that temazepam treatment at night improved sleep by reducing the duration of awakenings and time spent in the most superficial sleep stages. Reduced body motility during sleep was also seen during treatment, and possibly the improvement in sleep induced by the drug contributed to this reduction. It was concluded that temazepam may be used as an effective short-term hypnotic in these patients. On the other
hand, DeNucci et al. (1998) used triazolam in the treatment of patients with orofacial pain and although subjective effect on sleep was seen, no effect on pain was observed. This may, however, be related to the increase in NREM 2 induced by benzodiazepine hypnotics.

During the latest years, third-generation hypnotics have been developed that are characterized by fewer side effects (Goa and Heel, 1991) and minor changes in sleep structure. Drewes et al. (1991) conducted a study with zopiclone in patients with fibromyalgia. An improvement in daytime tiredness and subjective sleep-related complaints was found, although no effect on pain outcome parameters was observed. Sleep structure was not changed during active treatment. Imidazopyridine hypnotics, which probably have more selective receptor specificity, were also found to improve sleep and daytime energy in fibromyalgia, although no effect on pain was seen (Moldofsky et al., 1996).

In patients with rheumatoid arthritis, previous reports on hypnotics in the treatment were based on first- or second-generation drugs. Although a positive effect of these drugs was seen in pilot studies, Hart et al. (1970), in an early report, found hypnotics unpopular due to aggravation of morning stiffness. Walsh et al. (1996) used triazolam for night treatment in patients with rheumatoid arthritis selected according to subjective complaints of fatigue or sleepiness and difficulties with sleep onset. There was a reduction in daytime sleepiness with improvement in the subjective sleep score and morning stiffness in comparison with placebo treatment. A trend towards an improvement in pain score was seen, but there were no differences in the other arthritis scales. It was concluded that short-term therapy with hypnotics may be of benefit in selected patients. In the study by Drewes et al. (1998b), however, only subjective improvement of sleep was found, but no differences in pain score or the other clinical parameters were seen. Conventional sleep assessments showed only minor changes during treatment, but frequency analysis demonstrated a shift from the lower towards the higher EEG frequencies in the active treatment group. Although the modulation of the EEG can represent a non-specific pharmacologic epiphenomenon, it might also reflect a disturbance of sleep microstructure. Thus, treatment with newer hypnotics may be of value for subjective sleep complaints in selected patients with pain, but it is doubtful whether these drugs improve daytime symptoms in pain patients. Newer, experimental treatment regimes such as antidiencephalon immune serum or gamma-hydroxybutyrate may improve sleep and pain together with daytime symptoms (Kempanaers et al., 1994; Scharf et al., 1998), but further controlled studies are needed to confirm these results.

**CONCLUSION**

In summary, sleep disturbances are frequent in patients with pain, and the complex interaction between pain and sleep may be responsible for many of the daytime symptoms in these patients. Analgesics, such as acetaminophen, may not alter sleep structure in healthy subjects, whereas aspirin and NSAIDs could have negative effects. Pain patients are a heterogenous group and treatment with analgesics may not have the same effects in the different patients. For example, in rheumatoid arthritis, NSAIDs do not seem to give objective sleep changes, whereas the subjective feeling of sleep may improve. During amitriptyline and opioid treatment, a negative sleep profile may be induced which can limit the use of these drugs in pain patients. Hypnotics are frequently used in pain patients. Hypnotics may be of some value, as improvement in sleep and daytime energy is crucial to these patients. Pain, however, is probably only affected to a minor degree and additional treatment must frequently be recommended. Medication supposed to have more selective receptor subtype specificity or experimental substances may turn out to be useful. Future studies are highly recommended in this area and should rely on controlled, objective experiments where polysomnography is performed together with signal analysis of the EEG microstructure. Disturbed sleep and related daytime symptoms are often neglected complaints in medical patients suffering from pain. The clinician should be aware of these possible interactions and consider directing the treatment against the nightly complaints.

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