Special Considerations in Insomnia Diagnosis and Management: Depressed, Elderly, and Chronic Pain Populations

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Patients with insomnia who also have chronic pain or depression or who are elderly represent segments of the population that are particularly difficult to treat. These populations tend to be at higher risk for experiencing difficulty sleeping and are more likely to experience chronic insomnia, sleep maintenance problems, and/or nonrestorative sleep. Worsening insomnia may exacerbate other somatic and psychological symptoms and vice versa. Conversely, there is evidence that appropriate recognition and management of the sleep complaint may alleviate other symptoms related to the associated condition and help interrupt this vicious cycle. *(J Clin Psychiatry 2004;65[suppl 8]:26–35)*

Insomnia is experienced by many people, with between 20% and 40% of the adult population in the United States experiencing sleep difficulties that range from the transient and occasional to the chronic and severe.[1–4] However, there are certain populations that are particularly prone to developing sleep difficulties, including individuals with depression, those with chronic pain syndromes, and the elderly. Sleep disturbances in these groups are usually chronic,[5–8] and, as a result, they are usually more difficult to treat, because currently prescribed hypnotic agents are recommended for short-term use only (i.e., generally 1 month or less).[9] Adequately addressing sleep disturbance is particularly relevant for these special patients, as there is some evidence that the presence of insomnia is associated with greater severity of a patient's primary condition.[10–12] This article addresses each of these populations and how their complicating conditions impact the recognition and treatment of insomnia.

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SPECIAL CONSIDERATIONS IN INSOMNIA ASSOCIATED WITH DEPRESSION

Depression is a common illness in the United States, with estimated lifetime prevalence in the general population of about 17%.[13,14] Sleep disturbance is frequently a symptom of depression and is part of the diagnostic criteria for a major depressive episode (DSM-IV). The association between depression and disturbed sleep has been well documented in both clinical and epidemiologic studies.[1,15–18]

Linking Insomnia and Depression

Frequent or severe insomnia occurs in 10% to 15% of the adult population[1,15,19–21] and has been associated with a host of psychological difficulties. A community survey of 3161 adults conducted by Mellinger et al.[1] found that 17% of their sample reported serious insomnia; subjects with any insomnia were more likely to have higher levels of psychic distress, with the highest rate (47%) in the group of serious insomniacs. Several other epidemiologic studies have found that insomnia is associated with a reduced capacity for dealing with stress.[22,23] Psychological disturbance is not necessarily limited to insomnia with a psychological etiology; Kalogjera-Sackellares and Cartwright[24] compared rates of psychopathology between subjects with medically induced insomnias (e.g., related to sleep apnea) and those with psychologically induced insomnias (Diagnostic Classification of Sleep and Arousal Disorders criteria), and found that both groups were equally likely to have elevated scores on the Minnesota Multiphasic Personality Inventory (a measure of psychological functioning, in which higher scores correspond to increasing pathology).

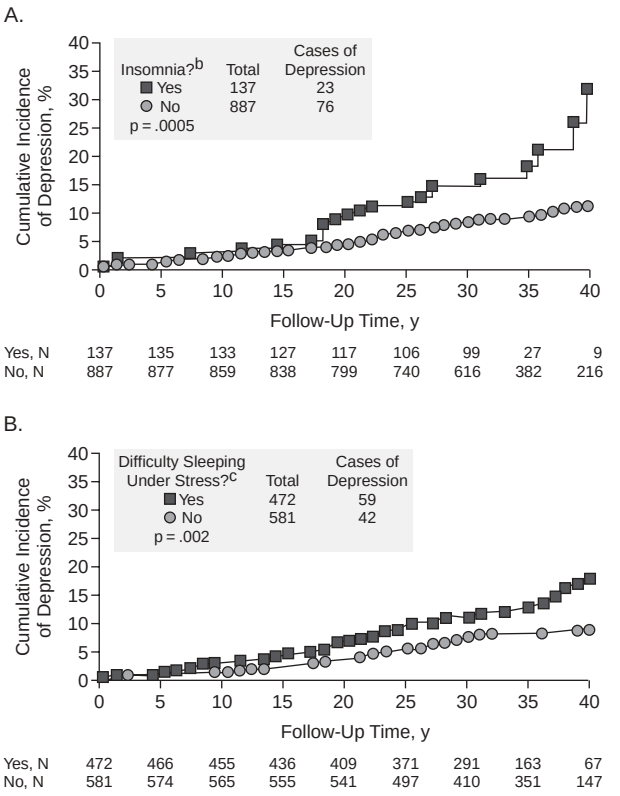
Epidemiologic studies have also found that insomnia is associated with a higher prevalence of psychiatric disorders. Depression or anxiety was reported by 34% of subjects with serious insomnia in the Mellinger et al.[1] community survey, compared with only 12% of subjects without insomnia. Similarly, the National Institute of Mental Health (NIMH) conducted an epidemiologic study in 7954 adults[15] and found that 40% of subjects who reported insomnia over the past 6 months also met criteria for a psychiatric disorder, compared with only 16% of those who did not report insomnia. Breslau et al.[17] determined that the lifetime prevalence of insomnia in young adults (N = 1007) was 25% overall. Among insomniacs, the lifetime prevalence of a psychiatric disorder was 71%, compared with 41% among normal sleepers (odds ratio [OR] = 3.5). The OR for depression with insomnia was 16.6 but was even higher when mixed symptoms of both insomnia and hypersomnia were present (OR = 41.8).[17]

A number of studies have found that clinical populations of insomniacs have higher rates of psychiatric comorbidity than do those without insomnia. Over 75% of insomnia patients who were evaluated at a sleep center received a primary or secondary diagnosis of insomnia related to psychiatric disorders (the breakdown of psychiatric diagnoses was not specified) in a multicenter study by Buysse et al.[25] In a primary care setting, it is estimated that 50% to 69% of patients with insomnia have a psychiatric disorder.[3,26,27] Within medical populations, insomnia is more strongly associated with major depression than with other medical disorders.[26] Furthermore, women have been found to have higher rates both of insomnia and of anxiety or depression. This observation has been attributed to gender effects on the prevalence of anxiety and depression and not to a gender effect on sleep per se.[28]

Insomnia Predicts Depression

The NIMH epidemiologic survey found that disturbed sleep was a predictor for developing a psychiatric illness; the odds of developing depression were 39.8 if insomnia was experienced during the preceding year, but those odds were only 1.9 if the insomnia had resolved during that time.[15] Several other studies have found that disturbed sleep is often a harbinger of depression. In a study of 1024 nondepressed men in medical school who were followed for up to 45 years (median = 34 years), insomnia was reported by 137 men, while 887 reported no insomnia.[18] During follow-up, the cumulative incidence of depression was 12.2% (N = 101). Self-reported insomnia and difficulty sleeping under stress were found to be associated with an increased risk for developing depression later in life (Figure 1), as were poor sleep quality and nightly sleep duration of 7 hours or less. After controlling for other potential risk factors for depression, including family history, age, temperament type, and tobacco and alcohol use, self-reported insomnia ($p < .01$) and difficulty sleeping under stress ($p < .05$) in young adulthood were still seen to strongly predict the subsequent development of depression.

Figure 1. Cumulative Incidence of Depression in Men With Insomnia (A) and Difficulty Sleeping Under Stress (B)[a]



[a]Reprinted with permission from Chang et al.[18] Cumulative incidence of depression in 1045 men according to sleep complaints in medical school. The numbers below each Kaplan-Meier plot are the numbers of men included in the analysis at each timepoint.
[b]Cumulative incidence of clinical depression over 44 years of follow-up in those who reported insomnia vs. those who did not was 31.6% vs. 10.4%, respectively ($p < .001$).
[c]Cumulative incidence of clinical depression over 44 years of follow-up in those who reported difficulty sleeping under stress vs. those who did not was 17.7% vs. 8.4%, respectively ($p < .005$).

Several studies have also found that insomnia predicts depression in elderly adults.[29–31] Furthermore, insomnia has been found to be a precursor to the recurrence of depression in patients in clinical remission: the symptoms of sleep disturbance and fatigue preceded the onset of other depressive symptoms including dysphoria, dissatisfaction, crying, and irritability.[32] In fact, Breslau et al.[17] found that sleeping difficulty alone has been found to predict depression, even in the absence of other depressive symptoms (OR = 2.1).

Insomnia has also been linked to mania. In a subgroup of patients with bipolar disorder who also had insomnia (77%), insomnia was found to be the most robust early predictor of an impending manic episode.[33] Prodromes

Table 1. Objective Changes in Sleep in Depressed Patients

Reduction in sleep continuity
Decreased total sleep time
Decreased sleep efficiency
Increased sleep latency
Loss of slow-wave sleep
Altered rapid eye movement (REM) patterns
Reduced REM latency
Increased percent time spent in REM
Increased REM activity (eye movements per minute of REM sleep)
REM shifted to earlier in the sleep period

Table 2. Sleep in Patients With Psychiatric Disorders Versus Controls[a]

Disorder	Sleep Continuity	Slow-Wave Sleep, %	REM Latency	Percent REM
Affective Disorder	↓	↓	↓	↑
Anxiety	↓	•	•	•
Schizophrenia	↓	•	↓	•
Eating disorder	↓	•	↓	•
Alcoholism	↓	↓	•	↑
Insomnia	↓	↓	•	•

[a]Data from Benca et al.[16]
Abbreviation: REM = rapid eye movement. Symbols: ↑ = parameter increased unequivocally relative to controls, ↓ = parameter decreased unequivocally relative to controls, • = no change in parameter relative to controls, ↑ = parameter increased in some studies relative to controls, ↓ = parameter decreased in some studies relative to controls.

predictive of the onset of a depressive episode in this group of bipolar patients were found to be shorter and more variable in presentation.

Depression Predicts Insomnia

The relationship between insomnia and depression appears to be bidirectional: there is not only evidence suggesting that insomnia may be a predictor of depression, but also that depressed mood may be a predictor of insomnia.[34] There is both objective and subjective evidence that sleep is disturbed in depressed patients. Table 1 shows a number of objective changes in sleep that have been observed in patients with depression. In a meta-analysis by Benca and colleagues,[16] sleep changes associated with psychiatric disorders including mood disorder, anxiety, schizophrenia, eating disorder, alcoholism, and insomnia were assessed (Table 2). Patients with mood disorders were found to have more robust changes across more sleep parameters than did patients with other disorders or healthy controls.[16] Polysomnographic recording in depressed patients has also shown the intrusion of alpha activity into delta sleep.[35]

Subjective assessments of sleep in patients with depression tend to confirm objective measures. Depressed patients have been found to underestimate the amount of sleep they have had, and this phenomenon has been correlated with severity of depression.[36] This phenomenon also raises the interesting question of the true nature of improved sleep with treatment of depression: does the insomnia complaint resolve because sleep is actually improved, or does it resolve because the patient's perception of his sleep is improved? Reynolds et al.[37] assessed 30 elderly patients with recurrent depression both during an acute episode (baseline) and during symptomatic remission following treatment. Despite improvements in reported sleep, subjective sleep quality during clinical remission in depressed patients still did not reach levels reported by age- and sex-matched healthy controls.[37] Objective measures with polysomnographic recording confirmed the subjective reports. Although state markers (e.g., sleep continuity, rapid eye movement [REM] density) improved, sleep did not return to normal. In contrast, trait markers (e.g., shorter REM latency, increased REM volume, loss of slow-wave sleep) persisted even during depressive remission.[37] In clinical experience, this persistence of both subjective and objective sleep disturbance suggests that patients with depression may require long-term insomnia treatment between depressive episodes.

Another possible reason that patients with depression are at a higher risk for insomnia is that many medications used to treat depression may disturb sleep. For example, the selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, paroxetine, and citalopram, have been found to increase REM latency, suppress REM sleep, cause eye movements during non-REM sleep, and decrease sleep efficiency.[38–41] Similarly, venlafaxine (a serotonin and norepinephrine reuptake inhibitor)[42] and stimulants such as modafinil[43] are associated with insomnia. The characteristics of sleep changes caused by these agents include decreased total sleep time and REM sleep, more nighttime arousals, and increased nighttime motor activity.

As well as altering polysomnographic sleep, certain medications can cause other physiologic changes during sleep. Antidepressants have been associated with periodic limb movement disorder.[41] Medications, including the benzodiazepines, have been shown to exacerbate obstructive sleep apnea,[44,45] and weight gain, which is a side effect of many psychiatric drugs,[46–48] also worsens obstructive sleep apnea.

Summary and Future Directions

There is a clear association between depression and insomnia, but a number of important clinical issues remain to be elucidated. One key question is how primary insomnia differs from insomnia associated with a psychiatric disorder and what such differences mean in terms of optimal treatment of insomnia in psychiatric patients. Given that objective and subjective sleep disturbance in patients with depression often extends into periods of clinical remission of the depression, the role of long-term treatment of insomnia for symptomatic relief must be established. Finally, the impact of treating an insomnia complaint on

the likelihood of developing first-onset depression or experiencing depressive relapse is a key question that must be addressed to guide treatment approaches to insomnia in depression.

SPECIAL CONSIDERATIONS IN INSOMNIA IN THE ELDERLY

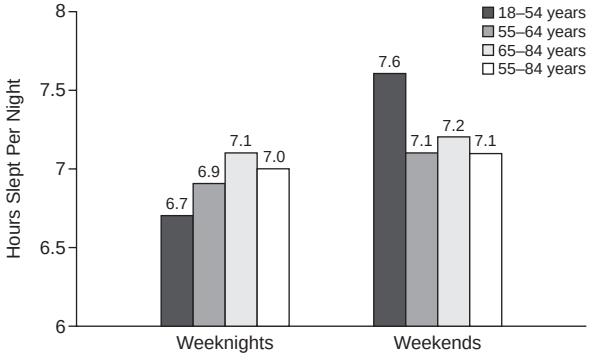
The number of elderly adults in the United States is rising. The 2000 U.S. census counted 35.0 million people older than 65 years, an increase of 12% since 1990.[49] Epidemiologic studies among the elderly have estimated that they are disproportionately dissatisfied with their sleep as compared with younger adults.[50] In the general population, 36% of adults report having sleep difficulties, and 26% are frequent sufferers, experiencing insomnia symptoms for an average of 16 nights or more per month.[7,21] The National Institute on Aging's Established Populations for Epidemiologic Studies of the Elderly (EPESE) found that 42% of elderly adults frequently had difficulty falling asleep or maintaining sleep or woke up too early in the morning. The consequences of insomnia can be serious in older individuals and can include greater risk of accidents or falling,[51] poorer quality of life,[52] and higher rates of institutionalization.[53] Regardless of an individual's age, disturbed sleep results in a number of adverse outcomes, such as difficulty concentrating, slowed response time (which impacts driving ability), memory impairments, and decreased performance. However, all of these sequelae may be mistaken for dementia in elderly patients in the clinic, adding a layer of complexity to the diagnosis and management of insomnia in these patients.[54,55]

Given the higher prevalence of sleep loss in elderly populations and its potentially dangerous consequences, it is important to identify and address the special concerns regarding the clinical presentation and management of insomnia in the elderly.

Sleep Disturbances in the Elderly

The incidence of insomnia was estimated in a longitudinal study in which 6899 elderly subjects were assessed for symptoms of sleep disturbance at baseline and again at a 3-year follow-up.[34] An annual insomnia incidence rate of roughly 5% was found, with 15% of the 4956 subjects who had no sleep disturbance at baseline reporting symptoms after 3 years. The EPESE interviewed 9282 adults aged 65 years and older and assessed measures of sleep disturbance consisting of trouble falling asleep, awakening during the night, awakening too early, needing to nap during the day, and awakening feeling unrefreshed.[56] Sleep complaints were more frequent in subjects who had depressed mood, fair to poor health, respiratory symptoms (such as chronic coughing, wheezing, or phlegm), and physical disability, and in those who used medications such as anxiolytics or barbiturates. Those risk factors were also associated with all but 7% of incident cases of insomnia in the longitudinal study,[34] as well as with the majority of cases in which insomnia was retained at the 3-year follow-up. Remission of insomnia symptoms was reported by about 50% of subjects who had chronic insomnia at baseline and was associated with improved self-perceived health.[34] These findings suggest that insomnia in the elderly is not related to the aging process per se.

Figure 2. Reported Hours Slept: Older Versus Younger Adults[a]



[a]Data from National Sleep Foundation.[58] Older adults do not report sleeping fewer hours than younger adults.

As shown in Figure 2, the 2002[57] and 2003[58] Sleep in America polls, conducted for the National Sleep Foundation, found that, contrary to common perception, sleep behavior does not differ significantly between older adults (55 to 84 years) and younger adults (18 to 54 years). Specifically, older adults (N = 1506) did not report sleeping fewer hours per night than did younger adults (N = 710), and, in fact, younger adults were the group that reported sleeping the least, with a mean of 6.7 hours per night during the week. Older adults reported sleeping 7.0 hours per night. On weekends, while younger adults' sleeping time increased to 7.6 hours, older adults reported a sleep duration of 7.1 hours, similar to weekday reports.

Sleep problems were correlated with the prevalence in older individuals of medical conditions including heart disease, lung disease, and stroke and with psychiatric illnesses including depression. It was found that subjects with those conditions were more likely to sleep less than 6 hours per night, experience daytime sleepiness, or report at least 1 symptom of insomnia (i.e., difficulty falling asleep, waking a lot during the night, waking up too early and being unable to get back to sleep, and waking up feeling unrefreshed). Once again, these findings suggest that medical illness, rather than aging per se, is associated with sleep disturbance in older adults.

Many medical conditions are known to result in insomnia, and the number of medical diagnoses an individual has tends to increase with age.[58] Insomnia may be caused by conditions associated with chronic pain, such as ar-

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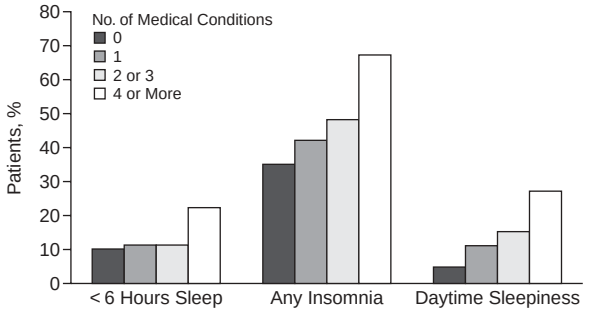
Figure 3. Sleep Problems and Multiple Medical Conditions[a]

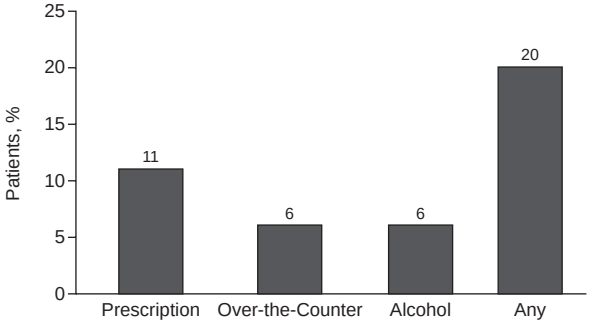


[a]Data from National Sleep Foundation.[58]

Table 3. Drugs That Cause Insomnia

Alcohol
Decongestants
Central nervous system stimulants
Stimulating antidepressants
Beta-blockers
Thyroid hormones
Bronchodilators
Nicotine
Calcium channel blockers
Caffeine
Corticosteroids

Figure 4. Use of Substances to Promote Sleep in the Elderly[a]



[a]Data from National Sleep Foundation.[58] The use of sleep aids is common in the elderly, with prescription medications used most frequently.

thritis and cancer; neurologic disorders, such as restless legs syndrome and Alzheimer's and Parkinson's diseases; and organ system dysfunctions such as angina, asthma, chronic obstructive pulmonary disease, and gastrointestinal reflux.[59] The 2003 Sleep in America poll[58] found that there is a linear relationship between sleep problems and the number of medical diagnoses a subject has (Figure 3), with a greater number of medical conditions conferring a greater likelihood of sleeping less than 6 hours per night, having at least 1 symptom of insomnia, or experiencing daytime sleepiness. Elderly adults who reported having 4 or more medical conditions had higher rates of sleep difficulties than did those with fewer conditions. Twenty-two percent of subjects with 4 or more medical conditions reported sleeping less than 6 hours per night compared with 10% of those with no medical conditions. Similarly, 67% of subjects with 4 or more conditions versus 35% with no conditions reported insomnia, and 27% of subjects with 4 or more conditions versus 5% with no conditions reported daytime sleepiness. Furthermore, multiple medical conditions increased the probability of experiencing unpleasant tingling feelings in the legs or having a diagnosis of a sleep disorder.[58]

Treating Insomnia in the Elderly

Because older individuals frequently have multiple medical conditions, they are also often managed with polypharmacy. A treatment regimen including multiple drugs may increase the risk for insomnia, since many drugs are known to cause sleep disturbance as a side effect (Table 3). The 2003 Sleep in America poll[58] found that 20% of older adults use sleep-promoting agents, including prescription medications, over-the-counter drugs, and alcohol, a few nights per week or more in order to help them sleep (Figure 4); 15% reported using a sleep aid every night or almost every night. The chronic use of sleep-promoting agents is higher in the elderly than in younger adults; 6% of younger adults reported using a prescription medication and 5% reported using an over-the-counter agent at least a few times per week, compared with 11% and 6% of older adults who take prescription and over-the-counter medications, respectively. However, due to differing drug metabolism associated with aging, caution should be used in administering pharmacotherapy in the elderly,[60] and nonpharmaceutical approaches, such as education regarding proper sleep hygiene and other behavioral methods, are recommended as supportive therapies.[54,60,61]

Summary

In summary, conditions or circumstances that are frequently faced by older adults such as medical illness and polypharmacy can result in insomnia. These data suggest that although insomnia is very common in elderly populations, it does not appear to be intrinsic to the aging process itself.

SPECIAL CONSIDERATIONS IN INSOMNIA ON NONRESTORATIVE SLEEP ASSOCIATED WITH CHRONIC PAIN AND FATIGUE

Chronic pain is associated with a high insomnia prevalence.[71] Pain appears to worsen sleep difficulties, and sleep difficulties appear to worsen the perception of pain.[87] Patients with pain syndromes experience the gamut of insomnia symptoms, with high rates of sleep maintenance

problems, sleep onset problems, and reports of nonrestorative sleep. Elucidating the link between pain and insomnia can help guide treatment decisions and alleviate patient suffering. This brief review is not intended to be comprehensive and will be limited to a discussion of the pain associated with rheumatologic conditions and its relation to nonrestorative sleep.

Prevalence of Insomnia/Nonrestorative Sleep in Patients With Chronic Pain

DSM-IV describes 3 categories of sleep disturbance in the diagnostic criteria for insomnia[62]: difficulties in sleep onset (or initiation), difficulties in sleep maintenance, and nonrestorative sleep. The first 2 categories, difficulties in initiating and maintaining sleep, are the more commonly studied and are characterized by disturbances in the quantity of sleep. The third and less commonly studied category, nonrestorative sleep, is qualitative rather than quantitative in nature. Nonrestorative sleep is particularly frequent among individuals with complaints of chronic musculoskeletal pain and with fatigue such as occurs with fibromyalgia or chronic fatigue syndrome (CFS).[64,76]

Insomnia has been associated with a number of chronic somatic health disorders, including chronic pain. An epidemiologic study of somatic diseases (including hypertension, obstructive pulmonary disease, and rheumatic disease) found that problems with sleep maintenance were as common as problems with initiating sleep (22.4% and 21.2%, respectively).[8] Fatigue-related disorders such as CFS[63] and fibromyalgia[64,65] have also been associated with disturbed sleep. In fibromyalgia, rates of sleep disorder range from 62% to 95%.[66–69] In CFS, the overall rate of sleep disorders in one study was 87% (including inadequate sleep hygiene in 69% of patients, restless legs syndrome in 35%, and sleep disorders associated with mood disorders in 28%),[63] and, in another study, 93% of patients experienced disturbed sleep.[66] Sleep maintenance difficulty was the primary sleep complaint of patients with CFS, regardless of the presence of a psychiatric disorder.[63] Tishler et al.[70] found that, in patients with the autoimmune disorder Sjogren's syndrome, the presence of fibromyalgia (in 36 of 65 patients) was associated with the presence of sleep disturbances (moderate or severe, found in 49 of 65 patients).

Conditions involving chronic pain are especially associated with disturbed sleep. In an analysis of cross-sectional data from the 1991 Canadian General Social Survey, Sutton et al.[71] found that, while subjects with chronic medical illnesses generally had increased likelihood of having insomnia ("trouble going to sleep or staying asleep"), the highest ORs were found with pain-related conditions, compared with conditions that are not as strongly characterized by pain, such as allergy, diabetes, and circulatory disease. For example, 38% of patients with rheumatic diseases experienced insomnia (OR = 2.45; 95% CI = 2.22 to 2.72) compared with 28% of patients with allergy (OR = 1.35; 95% CI = 1.23 to 1.49). Other studies have described a similar relationship between disturbed sleep and chronic pain. McCracken and Iverson[72] found that 88.9% of 287 patients seeking treatment in a pain clinic reported at least 1 sleep disturbance, and in patients with arthritis, there is a high prevalence (estimates approaching 60%) of restless sleep.[73–75]

Sutton et al.[71] found that insomnia was more likely to be experienced in the presence of pain in general; 44% of respondents who had pain reported insomnia, while only 19% of those with no pain reported insomnia. Increasing pain severity was associated with increasing risk for insomnia: Insomnia was reported by 19% of respondents reporting mild pain (OR = 2.28), by 42% of those reporting moderate pain (OR = 2.99), and by 58% of those reporting severe pain (OR = 5.73). There was a similar relationship between pain and the experience of nonrestorative sleep, which was reported by 34% of respondents with mild pain (OR = 1.58), by 43% of those with moderate pain (OR = 2.39), and by 51% of those with severe pain (OR = 3.35).[71]

Nonrestorative sleep has a high prevalence—the 1991 Canadian General Social Survey found that 24% of respondents reported that their sleep is refreshing only sometimes, and 3% reported that their sleep is never refreshing—and is associated with characteristic sleep and waking symptoms[76] (Table 4). Although there are a number of conditions that are associated with nonrestorative sleep, much of the work investigating the relationship between pain and this type of sleep disturbance has been conducted in fibromyalgia; thus, the discussion here will focus primarily on patients with fibromyalgia.

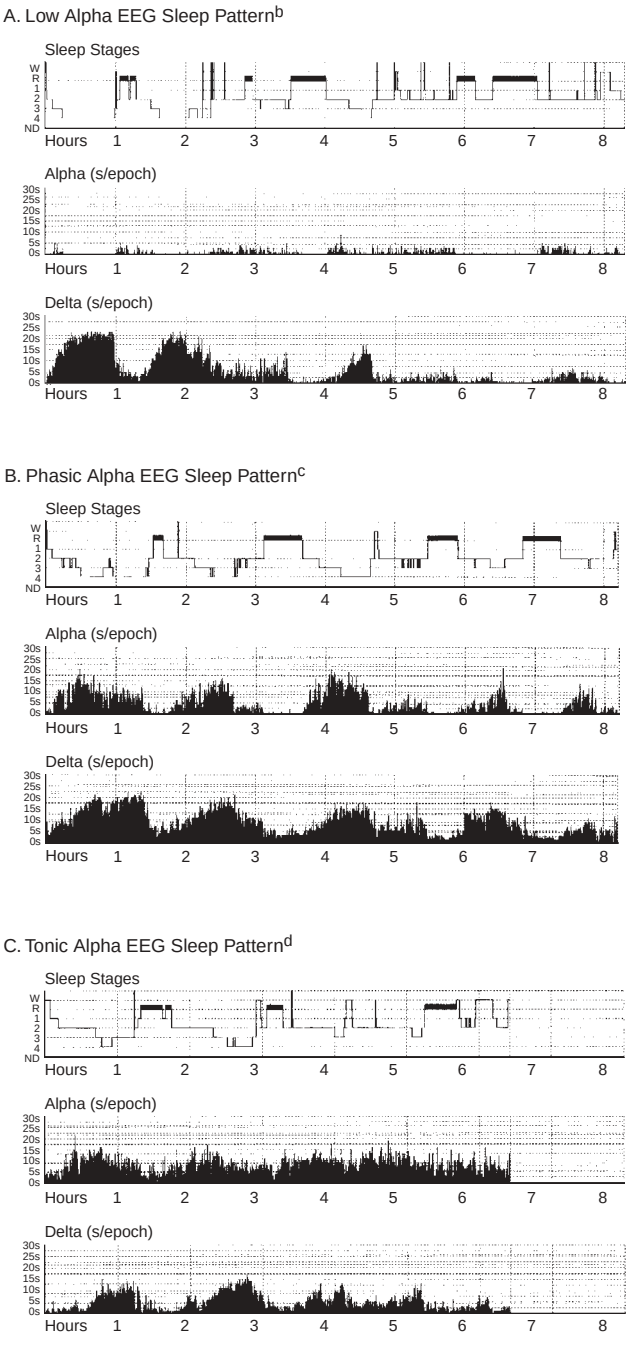
Table 4. Sleep and Wake Symptoms Associated With Nonrestorative Sleep

Sleep Symptoms
A feeling that sleep is light or superficial
A lack of feeling refreshed upon awakening
Wake Symptoms
Physical and mental fatigue
Variable nonspecific pain
Hypersensitivity to noxious stimuli
Dysphoria
Autonomic disturbances

Nonrestorative Sleep in Fibromyalgia

Nonrestorative sleep is one of the symptoms noted by the American College of Rheumatology in its 1990 criteria for fibromyalgia,[65] and there is a high prevalence of sleep disorders in both patients with fibromyalgia and patients with CFS. In fact, the behavioral symptoms that characterize fibromyalgia are similar to those that are described earlier in this review and listed in Table 4 characterizing nonrestorative sleep: sleep symptoms of light or superficial sleep or nonrestorative sleep and wake

Figure 5. Three Distinct Electroencephalographic (EEG) Patterns of Alpha Activity During Sleep[a]



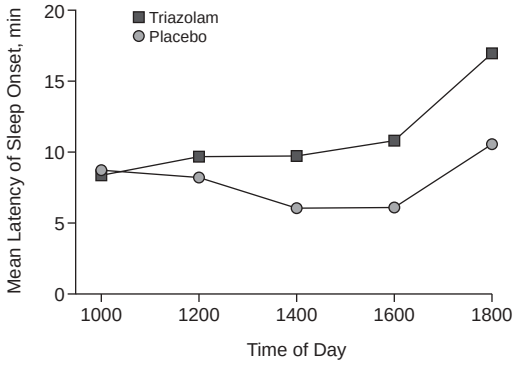
[a]Reprinted with permission from Roizenblatt et al.[77] The upper plot in each panel (sleep stages) is a hypnogram. The middle plot shows alpha activity during sleep, and the lower plot shows delta activity during sleep.
[b]This pattern is typical of the majority of healthy individuals.
[c]This pattern is characterized by an episodic alpha rhythm occurring concurrently with delta activity. It is a pattern observed in patients with fibromyalgia and is rare in healthy individuals.
[d]This pattern is characterized by the unremitting presence of alpha activity during non-REM sleep that is independent of delta activity. It is more common in patients with fibromyalgia than in healthy individuals.

symptoms of physical and mental fatigue; variable, nonspecific pain; autonomic disturbances; and psychological disturbances.[65]

Objective electroencephalogram (EEG) abnormalities that are associated with nonrestorative sleep have been observed in the sleep of patients with fibromyalgia.[77–80] Normal, refreshing sleep is characterized by low alpha EEG during slow-wave sleep[77] (Figure 5A). However, patients with fibromyalgia and nonrestorative sleep have increased alpha activity during non-REM sleep,[77–79] an increased alpha/delta power ratio,[78,80,81] and increased alpha and theta/delta time during slow-wave sleep (in children with fibromyalgia and their mothers).[82] This nonrestorative sleep in patients with fibromyalgia may exhibit tonic or phasic alpha patterns during slow-wave (alpha/delta) sleep[77] (Figures 5B and 5C), and may also exhibit periodic EEG sleep disturbances (such as frequent cyclic alternating patterns, including K-alpha or periodic polyphasic patterns, or disturbances accompanying periodic limb movements and periodic sleep apnea or hypopnea).[77,83] These phasic and tonic increases in EEG alpha activity during non-REM sleep occur in 80% to 90% of patients with fibromyalgia and CFS.[77,78] Frequent cyclic alternating patterns, periodic K-alpha, or polyphasic EEG bursts occur in 55% of patients; periodic limb movement syndrome occurs in 21%; and sleep apnea occurs in 3%. Furthermore, subjective muscular pain, increased tenderness, and fatigue were shown to be linked to poor sleep in early studies by Moldofsky et al.,[64,76] in which normal subjects had disruption of stage 4 sleep via auditory stimulation at the onset of slow-wave (deep) sleep. The emergence of pain and fatigue symptoms in healthy sleepers was repeated in subsequent experimental studies of disruption of slow-wave sleep with nonspecific auditory arousals.[84,85]

Wolfe et al.[86] characterized the clinical features and predictors associated with fatigue in 1488 patients with rheumatic disease, including rheumatoid arthritis, osteoarthritis, and fibromyalgia. They found that fatigue was reported by 88% to 98% of patients. Fatigue occurred in 41% of patients with rheumatoid arthritis or osteoarthritis and in 76% of those with fibromyalgia. Sleep disorder, depression, and pain were among the strongest independent predictors of fatigue, with these features accounting for roughly 90% of the variance of fatigue (R^2 for all patients = 0.51, rheumatoid arthritis = 0.49, osteoarthritis = 0.45, fibromyalgia = 0.41). Affleck et al.[87] conducted a 30-day study of fibromyalgia subjects and showed that poorer sleepers report more pain: The poorer sleep is on a given night, the more pain will be experienced the following day. Conversely, the more pain experienced during the day, the poorer that night's sleep will be. Similarly, Nicassio et al.[88] showed that a dysfunctional cyclical pattern of heightened pain and nonrestful sleep underlies the experience of fatigue in fibromyalgia patients; thus, poor sleep quality can be seen to mediate pain and fatigue.

Figure 6. Mean Multiple Sleep Latency Test (MSLT) Scores After 6 Nights of Treatment With Triazolam in Patients With Rheumatoid Arthritis[a]



[a]Reprinted with permission from Walsh et al.[95] Mean latencies of onset to sleep on the MSLT were longer with triazolam than with placebo. Differences were significant at 1400, 1600, and 1800 hours.

Management

Appropriate treatment of the symptoms of sleep disturbance is an important component to managing patients with chronic pain or fatigue. Clinical assessment of sleep disorders should include an interview of both the chronic pain patient and a family member to ascertain sleep habits and symptoms that include the quantity and quality of sleep, number of awakenings, presence of snoring, and restlessness or movement of limbs, as well as daytime waking behavior such as energy, alertness, cognitive functions, and mood.[89,90] Behavioral assessments can be made using scales[91] such as the Sleep Assessment Questionnaire, which includes 6 sleep factors: insomnia/hypersomnia, nonrestorative sleep, sleep-schedule disorder, excessive daytime somnolence, sleep apnea, and restlessness.

To objectively clarify the complaint of nonrestorative sleep—especially for determining tonic or periodic EEG sleep disturbances (i.e., frequent cyclic alternating patterns, sleep apnea, periodic movements in sleep) or if the diagnosis is unclear—the patient may be referred to a comprehensive sleep clinic for polysomnography and clinical assessment by a sleep medicine specialist.[89,90] The Multiple Sleep Latency Test (MSLT) is useful for differentiating daytime sleepiness from physical and mental fatigue.[90]

A number of nonspecific treatments can be used in managing nonrestorative sleep. Behavioral methods that may be useful in fibromyalgia and CFS include cognitive-behavioral psychotherapy,[90,92,93] sleep hygiene,[90,92] and a suitable aerobic fitness program.[90] These methods may also be beneficial in the treatment of rheumatoid arthritis and other chronic pain conditions.[93,94] Among pharmacologic treatments, triazolam has been shown, in a double-blind, placebo-controlled crossover study in patients with rheumatoid arthritis, to improve measures of sleep, daytime sleepiness, and morning stiffness.[95] Mean latencies to onset of EEG sleep, as measured by the MSLT, were longer after treatment with triazolam than with placebo (Figure 6). While tricyclic agents such as amitriptyline[96–98] improve sleep, they do not reduce the EEG abnormalities associated with sleep-arousal disorders such as alpha activity during non-REM sleep.[99] Similarly, the nonbenzodiazepine hypnotics zolpidem[100] and zopiclone,[101] and investigational agents such as 5-hydroxy-L-tryptophan[102] and growth hormone,[103] may improve sleep quality, but their impact on EEG sleep disturbances is uncertain. Sodium oxybate, a form of gamma hydroxybutyrate, is reported in one randomized, double-blind, placebo-controlled study to improve pain, fatigue, and nonrestorative sleep by reducing the EEG alpha activity and increasing slow-wave sleep in patients with fibromyalgia.[104] Large-scale studies are required to verify these important findings.

Summary

Pain (such as that associated with rheumatologic conditions) and nonrestorative sleep appear to mutually exacerbate one another, such that sleep disturbance worsens a patient's pain, and pain worsens a patient's sleep disturbance. In patients with fibromyalgia, there is evidence that this bidirectional link between nonrestorative sleep and chronic musculoskeletal pain and fatigue may be mediated by characteristic EEG abnormalities such as the alpha EEG sleep disorder and periodic EEG sleep disturbances (i.e., frequent cyclic alternating pattern, sleep apnea, and periodic limb movements). While symptomatic control of acute pain helps to alleviate insomnia, the chronic musculoskeletal pain and fatigue may in turn be successfully managed with treatment of coincident poor-quality sleep.

CONCLUSIONS

The diagnosis and treatment of insomnia, which is always challenging, is more complicated in individuals with medical or psychiatric illness and in the elderly. Not only do these populations have higher rates of insomnia than do healthy, younger adults, but they are also more likely to have persistent and difficult-to-treat symptoms, such as sleep-maintenance problems. Although treating primary conditions such as depression, chronic pain, or illnesses associated with aging may help alleviate insomnia symptoms indirectly, adequate pharmacologic and behavioral therapy targeted to the sleep disturbances themselves are important in these patients. To that end, gaining a better understanding of the underlying pathophysiology associated with insomnia and identifying the associated risk factors will help improve diagnosis, allow for better treatment decisions, and aid in the development of new therapies.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), fluoxetine (Prozac and others), modafinil (Provigil), paroxetine (Paxil and others), sertraline (Zoloft), sodium oxybate (Xyrem), triazolam (Halcion and others), venlafaxine (Effexor), zolpidem (Ambien).

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