Diagnosis and Management of Insomnia in Dialysis Patients

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ABSTRACT

Sleep-related complaints affect 50–80% of patients on dialysis. Sleep disorders impair quality of life significantly. Increasing evidence suggests that sleep disruption has a profound impact both on an individual and on a societal level. The etiology of sleep disorders is often multifactorial: biologic, social, and psychological factors play a role. This is especially true for insomnia, which is the most common sleep disorder in different populations, including patients on dialysis. Biochemical and metabolic changes, lifestyle factors, depression, anxiety, and other underlying sleep disorders can all have an effect on the development and persistence of sleep disruption, leading to chronic insomnia. Insomnia is defined as difficulty initiating or maintaining sleep, or having nonrestorative sleep. It is also associated with daytime consequences, such as sleepiness and fatigue, and impaired daytime functioning. In most cases, the diagnosis of insomnia is based on the patient's history, but in some patients objective assessment of sleep pattern may be necessary. Optimally the treatment of insomnia involves the combination of both pharmacologic and nonpharmacologic approaches. In some cases acute insomnia resolves spontaneously, but if left untreated, it may lead to chronic sleep problems. The treatment of chronic insomnia is often challenging. There are only a few studies specifically addressing the management of this sleep disorder in patients with chronic renal disease. Considering the polypharmacy and altered metabolism in this patient population, treatment trials are clearly needed. This article reviews the diagnosis of sleep disorders with a focus on insomnia in patients on dialysis.

Sleep problems are among the most frequently encountered complaints in dialysis units: several studies suggest that 50–80% of the patients with end-stage renal disease (ESRD) complain of sleep-related problems, including insomnia, restless legs syndrome (RLS), periodic limb movements in sleep (PLMS), and sleep apnea syndrome (SAS). Although much less information is available about the prevalence of sleep disorders in the chronic kidney disease (CKD) population not yet on dialysis, or in patients living with a functioning renal transplant, there is evidence that disorders of sleep and wakefulness are frequent in those populations as well. This two-part review focuses on patients managed with maintenance dialysis. As ESRD represents one specific stage in the spectrum of CKD, we feel it is important to include some information on sleep problems in the predialysis and transplanted populations as well. Here, we discuss issues related to sleep disorders in general and insomnia in particular. A subsequent article will describe sleep apnea and RLS.

Sleep disorders disrupt the normal sleep-wakefulness cycle, causing a distorted and fragmented sleep pattern, and leading to insufficient quantity or quality of restorative sleep, impaired daytime functioning, tiredness, fatigue, and sleepiness. Certain sleep disorders (e.g., sleep apnea) cause excessive daytime sleepiness (EDS). Recent data suggest a potential link between sleep problems and quality of life, and even increased mortality (1–5). Sleep apnea syndrome may have a special significance, as it may to contribute to cardiovascular morbidity and mortality in ESRD patients (6,7). Sleep apnea might also play a role in the development of specific symptoms, including cognitive impairment, fatigue, and other neuropsychiatric problems, which are more typically attributed to uremia.

Sleep disorders are associated with impaired quality of life, increased morbidity, hospitalization, and increased mortality (3–5,8–10). It has been shown that sleep problems are also associated with significantly increased utilization of health care resources (11–13). Sleep disorders in CKD patients are much more common than in the general population and contribute to poor outcomes (3,10,14–18). Unfortunately these disorders often remain undiagnosed and untreated. The goal of this

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review is to raise awareness among professionals involved in the management of dialysis patients and to provide guidance in recognizing and treating these important conditions.

Factors Contributing to the Increased Prevalence of Sleep Problems in Patients with Kidney Disease

Biochemical and pathophysiologic mechanisms, psychological problems, lifestyle, and treatment-related factors all contribute to the greatly increased prevalence of sleep disorders in patients with chronic renal disease (Table 1). The potential role of uremia-related factors (uremic toxins, acid-base disturbances) is supported by the substantial reduction in the prevalence of certain sleep problems after renal transplantation (19,20) and in patients treated with daily nocturnal dialysis (21). Renal anemia and iron deficiency have been linked to RLS and PLMS (22). Alterations in melatonin metabolism are detected in patients with renal failure (23) and may contribute to the pathogenesis of insomnia. Many of the drugs that are regularly used in CKD patients (e.g., β-blockers, steroids, calcineurin inhibitors, etc.) are known to interfere with sleep (24).

There is a relatively well-documented, complex association between depression and insomnia (25): insomnia may be one of the leading symptoms of depression. On the other hand, untreated insomnia can potentially lead to depression, anxiety, alcoholism or other psychological problems, or psychiatric disorders (26). Anxiety and overwhelming worries about the outcome of the disease, financial difficulties, family issues, and sexual dysfunction all contribute to impaired sleep in the patient population. Sedentary lifestyle, timing of dialysis treatments (such as early morning or late night dialysis, and long waiting and travel times to and from the dialysis unit) will also have a negative effect on sleep in dialysis patients.

Diabetes, the single most frequent cause of ESRD in North America and Europe, is also associated with various sleep disorders (27). Recently it has been shown that sleep duration of 6 hours or less or 9 hours or more is associated with increased prevalence of diabetes mellitus and impaired glucose tolerance (28). Obesity and neuropathy are pathogenetic factors for both SAS and RLS. Chronic pain associated with disease or treatment-related factors and with renal bone disease is probably one of the most important factors leading to chronic insomnia in dialysis patients.

TABLE 1. Potential pathogenetic factors of sleep disorders in patients with renal impairment

Pathophysiologic factors:
Disorders of acid-base metabolism
Electrolyte disturbances
Iron deficiency
Uremic toxins (small and middle molecules)
Renal anemia: decreased sensitivity of chemoreceptors
Renal neuropathia
Hypervolemia
Potential sleep-promoting factors that are "dialyzed out"
Medications
Altered melatonin metabolism
Psychological factors:
Mood disorders
Worries; anxiety
Sexual problems
Psychosocial problems (isolation, grief, financial strains, etc.)
Other psychological factors (dependence on the dialysis machine and the personnel; psychological effects of the transplantation)
Lifestyle-related factors:
Sedentary lifestyle
Staying in bed during the day, napping during dialysis
Getting up too early to get to dialysis in the morning
Other factors:
Alcohol and caffeine consumption
Smoking

Diagnosis of Sleep Disorders

Earlier studies in dialysis patients reported large variations in the prevalence of different sleep disorders. This can be attributed in part to the heterogeneity of the study populations, but also to differences in the criteria utilized to define sleep disorders. Furthermore, validated instruments to detect specific sleep disorders were not used in most of the early surveys assessing sleep complaints in ESRD patients.

Full polysomnography (PSG) is considered the "gold standard" for the diagnosis of most sleep disorders (29). However, it is not necessary in most of the patients with suspected insomnia or RLS, rather a clinical diagnosis is used (30). PSG is clearly needed for chronic, treatment-resistant cases, and in patients with hypersomnolence. Complete in-laboratory PSG traditionally involves monitoring sleep stages, respiratory effort, airflow, oxygen saturation (SaO_2), electrocardiogram (ECG), body position, and limb movements. Video monitoring may also be helpful, especially in the differential diagnosis of movement disorders and parasomnias. Sleep stages are monitored using two-channel electroencephalogram, electrooculogram, and a submental electromyogram. PSG is evaluated by scoring sleep stages, their distribution, the number and frequency of arousals from sleep, the number and frequency of apneas and hypopneas, limb movements, and body position. PSG is also used to titrate nasal continuous positive airway pressure (CPAP) therapy.

Polysomnography is a relatively expensive, time and labor intensive test and may not be feasible for large studies or for screening large patient populations. It may also be difficult to convince dialysis patients, already spending a substantial amount of their time each week attached to a machine in the dialysis center, to spend two nights in a sleep laboratory. To obtain reliable and comparable data in large populations, specific self-administered tools have been developed and validated to screen for insomnia, SAS, and RLS. These validated sleep questionnaires may be helpful for the assessment of sleep disorders in everyday clinical practice and also in epidemiologic studies.

Actigraphy (a small portable device attached to the wrist or leg that senses movement and stores the information) may be a useful tool in the objective evaluation of the sleep-wake (activity and rest) pattern (31). Home

video recordings and heteroanamnesis (information gained from the bed partner, a family member, or a friend) are especially useful in sleep-related movement disorders (e.g., PLMS) and in sleep apnea and parasomnias (e.g., sleepwalking).

Treatment of Sleep Disorders in CKD Patients

Although several studies address the prevalence and potential impact of sleep disorders in CKD patients (mainly dialysis patients), only very limited information is available regarding the therapy of sleep disorders in this population. There are very few nonpharmacologic and a limited number of pharmacologic studies reporting on the treatment of insomnia and sleep apnea. Only a few studies enrolling a limited number of patients have assessed the effectiveness of various medications in the treatment of RLS. This is particularly concerning, as patients with renal impairment pose significant problems when designing potentially long-term pharmacologic interventions for insomnia or RLS. The effect of renal impairment on the metabolism of a given drug is a very important consideration. Furthermore, CKD patients consume a large number of potentially interacting medications. Therefore drug interactions also need to be assessed carefully before introducing any new medications. The potential for tolerance and addiction with some of the hypnotics is also of particular importance.

Similarly, numerous questions arise when assessing nonpharmacologic therapies in CKD populations. The complex effects of chronic, potentially life-threatening kidney disease and the severely restrictive and intrusive CKD therapies will certainly require special considerations in designing psychological interventions, as these factors will influence patient compliance and the effectiveness of the interventions.

These special concerns can only be adequately addressed when results from appropriately designed and conducted randomized, controlled trials involving a large number of subjects with clinically important outcome measures, such as quality of life, morbidity, health care utilization, and even survival, are reported. Only then will it be possible to properly assess the effectiveness and overall value of individual treatment options in patients with renal impairment or on dialysis therapies. In the interim (as in this article), treatment options can be assessed through inferences from results obtained in various non-CKD populations.

Insomnia

Insomnia is characterized by one or more of the following symptoms: difficulty falling asleep ("sleep onset insomnia"), difficulty staying asleep ("sleep maintenance insomnia"), early morning awakening, or poor sleep quality ("nonrestorative sleep") (32). These sleep problems may lead to impaired daytime functioning, tiredness, fatigue, and sleepiness. Recently a consensus statement has recognized that insomnia is not only a symptom in some conditions, but also a comorbid condition in its own right (33). This statement also emphasizes that the term secondary insomnia may promote undertreatment and suggested the term "comorbid insomnia" instead. "Primary insomnia" implies that no other cause of insomnia has been identified.

Epidemiologic studies have utilized at least three different approaches to define chronic insomnia, resulting in vastly different estimates (6–50%) of the prevalence of the condition in the general population (32,34). The first approach assesses the presence of individual insomnia complaints. A second approach also takes daytime consequences of impaired sleep into account. More recently, large epidemiologic studies aimed at identifying patients who fulfill the diagnostic criteria for chronic insomnia outlined by the DSM-IV (e.g., SLEEP-EVAL) (35–38) or the International Classification of Diseases-10 (e.g., Athens Insomnia Scale [AIS]) (39,40). Data obtained with these latter two instruments suggest a comparable 6–9% prevalence in generally healthy adult populations in different countries (32,41).

Insomnia is 1.5–2 times more prevalent in women than in men in the general population, and is also associated with markers of social status. Insomnia is more common in persons with coexisting psychiatric and medical conditions, and in those suffering from chronic pain (32,41). It may also present secondary to underlying specific sleep disorders, like RLS, PLMS, and sleep apnea. Insomnia is associated with impaired quality of life (4,5,11) and increased morbidity and mortality (9). Insomnia is also independently associated with significantly more days of disability related to health problems, and increased use of health care resources (11,13).

Diagnosis of Insomnia

Insomnia is primarily a clinical diagnosis and it is most frequently diagnosed from data obtained from the history and from sleep diaries. PSG is not indicated in the initial evaluation of insomnia, but may be necessary in chronic, treatment-resistant cases and in patients in whom specific sleep disorders (SAS, RLS, PLMS) are suspected (30). History should include a review of sleep habits, drug and alcohol consumption, coexisting medical and psychiatric conditions, pain, and sleep environment. Heteroanamnesis from the bed partner or caregiver may complement useful information.

Specific points that should be asked include the onset, frequency, duration (transient, intermittent, or persistent), and severity of sleep complaints. In addition, the progression of symptoms, fluctuations over time, and any possible precipitating and perpetuating events should be investigated.

During the diagnostic interview questions about specific symptoms occurring around sleep onset (e.g., paresthesia or uncontrollable limb movements) and during sleep (e.g., frequent awakenings, loud snoring, or apneic episodes) should be asked. It is also important to know if the patient suffers from persistent early morning awakening. Frequent awakening may indicate the effect of certain drugs or underlying medical conditions. Early morning awakenings are frequently caused by anxiety or depression or by "relative drug withdrawal."

A sleep diary, completed by the patient, preferably over a 2-week period, often yields additional valuable information on sleep hygiene and on circadian rhythm sleep disturbances. A sleep diary will need to capture information on bedtime, daytime naps, time required to fall asleep, number and times of awakenings, total sleep time, and subjective evaluations of sleep quality as well as medications, washroom use, and other nighttime events and habits.

Insomnia in CKD Patients

Very little is known about the prevalence and risk factors of insomnia in renal patients. Iliescu et al. (42) found "poor sleep" using the Pittsburgh Sleep Quality Index (PSQI) in 53% of 120 prevalent CKD patients not yet on dialysis. Recently we also assessed the prevalence of RLS, SAS, and insomnia in 94 CKD patients not yet on dialysis using the AIS. The prevalence of insomnia in this population was 29%. Insomnia was significantly correlated with psychological distress and serum albumin, but not with the estimated glomerular filtration rate (GFR). Furthermore, insomnia was independently associated with impaired quality of life.

Several studies suggest that insomnia is substantially more prevalent in dialysis patients than in the general population. Earlier reports suffered from small sample size and most of these studies relied on nonvalidated tools to identify patients with insomnia (15,43–46). Sabbatini et al. (18) found insomnia symptoms in 45% of 694 dialysis patients. The authors concluded that elderly patients and those with a longer time on dialysis and with high levels of parathyroid hormone (PTH) were at higher risk of insomnia. In an earlier study of Hungarian dialysis patients, we identified 49% of patients complaining of at least one insomnia symptom (5).

Iliescu et al. (4) reported "poor sleep," defined by the PSQI, in 71% of patients on maintenance dialysis. More recently we identified 19% of wait-listed dialysis patients as suffering from clinically significant insomnia using the AIS, a validated instrument based on diagnostic criteria defined by the International Classification of Diseases-10 (10). Insomnia was associated with impaired quality of life and increased illness intrusiveness in some these studies.

Treatment of Insomnia in Renal Patients

The main goal of the treatment of insomnia is to improve subjective and objective sleep quality, to prevent sleepiness and fatigue usually associated with insomnia, and to improve daytime functioning. The effect of therapy can be assessed with quality of life instruments, sleep quality scales (PSQI, AIS), performance on attentional task tests, and other tests assessing different aspects of daytime functioning. Treatment of insomnia is unlikely to be successful over the long term without dealing with any underlying conditions. As a general rule in the management of secondary or comorbid insomnia, one should aim to treat any underlying disorders, such as chronic pain, itchiness, etc. If present, treating depression may improve insomnia symptoms as well.

TABLE 2. Sleep hygiene tips

Sleep only when sleepy. If you can't fall asleep within 20 min, get up and do something boring until you feel sleepy.
Don't take naps, unless your doctor advises so.
Regular sleep-wake schedule is important. Get up and go to bed the same time every day, even on weekends.
Regular exercise improves sleep, but most people should refrain from exercise at least 4 hr before bedtime.
Develop sleep rituals (listening to music, etc.). It is important to give your body cues that it is time to slow down and sleep.
Only use your bed for sleeping and intimacy. Refrain from using your bed to watch TV or work.
Stay away from caffeine-containing beverages, foods, and medications, nicotine, and alcohol at least 4–6 hr before bedtime.
Have a light snack before bed with a glass of milk, which contains sleep-promoting tryptophan.
Take a hot bath 90 min before bedtime. A hot bath will raise your body temperature, but it is the drop in body temperature that may leave you feeling sleepy.
Make sure your bed and bedroom are quiet and comfortable. Use appropriate curtains, earplugs, or a white noise machine if necessary. A cooler room is recommended. Use a humidifier if the air is too dry.

Increasing evidence supports the effectiveness of both nonpharmacologic and pharmacologic therapies for insomnia (47–51). Most studies assessing the effectiveness of different treatment modalities in insomniacs address short-term treatment of insomnia. Unfortunately most published information regarding the treatment of insomnia is restricted to individuals with no significant medical problems in general, and no renal impairment in particular.

Bearing all this in mind, we suggest that in most patients the mainstay of treatment should consist of behavioral measures in conjunction with the judicious use of hypnotics. Nonpharmacologic interventions include sleep hygiene measures, relaxation therapy and biofeedback, stimulus control therapy, sleep restriction, and cognitive behavioral therapy (33,51–54). These interventions have been shown to be beneficial in the long-term management of patients with chronic hypnotic use.

It is important to understand that successful treatment is only possible if the patient complies with suggestions to improve sleep hygiene (Table 2). These suggestions often combine several methods and may sound trivial. Compliance with such advice is still relatively poor, however, as it frequently requires changes in persistent "bad" habits which are ingrained. Building a regular sleep schedule and creating an appropriate sleeping environment, as well as regular physical activity, are very important in combating insomnia. Appropriate natural light exposure, even on cloudy days, can improve mood and also helps in maintaining a regular sleep-wake cycle. Napping is especially frequent in elderly people, but in some cases, it may also contribute to disrupted nighttime sleep. Napping during dialysis sessions should be avoided in patients prone to insomnia.

Cognitive behavioral therapy (CBT), using a combination of techniques, has been assessed in several small studies of patients with chronic insomnia. However, CBT has mostly been studied in patients with primary insomnia, and there is a need for additional randomized controlled trials to examine the efficacy of CBT for chronic insomnia in medically ill patients.

Cognitive behavioral therapy for insomnia in the routine general practice setting improved sleep quality, reduced hypnotic drug use, and improved health-related quality of life at a favorable cost in chronic insomniacs. Randomized controlled trials (RCTs) report somewhat conflicting results on the effectiveness of CBT in patients with insomnia, but one systematic review including six RCTs (282 people) found that group or individual cognitive behavioral therapy (including sleep hygiene, stimulus control, sleep restriction, muscle relaxation, and sleep education) significantly improved PSQI scores compared with no treatment, immediately after treatment, and at 3 months (50). Furthermore, another meta-analysis involving 2102 patients in 59 trials found that sleep restriction and stimulus control therapies were more effective than relaxation techniques when used alone (55). Structured exercise programs may also improve symptoms of insomnia (56). Despite the promise of CBT, the relative efficacy of these various nonpharmacologic approaches has not been well established. Data also suggest that CBT, in contrast to medications, may have a lasting effect beyond the termination of treatment. The extent to which the concomitant use of nonpharmacologic therapy augments the performance of pharmacologic treatments needs to be established in further studies.

Pharmacologic treatment is mostly indicated for transient insomnia. However, recent data support the feasibility of long-term pharmacologic management of chronic insomnia without evidence of tolerance or abuse (57,58). This concurs with our experience. At the same time only one of the eight medications (eszopiclone), approved by the FDA for the treatment of insomnia, has been approved for use without specified time-frame (33).

Although benzodiazepines (e.g., temazepam, flurazepam, triazolam, estazolam, quazepam, lorazepam, and clonazepam) are commonly used as hypnotics and have been shown to be efficacious in treating insomnia, they have also been associated with a number of adverse effects. These include tolerance, dependence, withdrawal and abuse potential, impairment in daytime cognitive and psychomotor performance (including an increased risk of accidents and falls), adverse effects on respiration, and the disruption of normal sleep architecture with a reduction in both slow wave sleep and rapid eye movement (59).

Benzodiazepine-receptor agonists (zolpidem, zaleplon, zopiclone, and eszopiclone) are also considered, along with the above benzodiazepines, first-line pharmacologic agents for the treatment of acute/transient insomnia. This second generation of hypnotics seems to have many advantages over the benzodiazepines (for a review of these issues see Montplaisir et al. (60)).

Based on the different profiles of these hypnotics, they might be indicated for sleep-onset insomnia (short acting) or maintenance insomnia (medium or long half-life). Short-acting drugs, such as triazolam and zaleplon, as well as zolpidem and zopiclone, are generally preferable because they produce less residual somnolence the morning following their use. Lorazepam and temazepam have a medium half-life, therefore they are considered mostly for maintenance insomnia. Longer acting agents (e.g., flurazepam), while improving sleep maintenance, may have significant residual effects (sedation, impaired cognitive and psychomotor function) that limit their use.

Although there is less clinical experience with the newer drugs, and we need more studies regarding their long-term use, the overall tolerability of the benzodiazepine-receptor agonists seems to be quite favorable, with a low propensity to cause clinical residual effects, withdrawal, dependence, or tolerance. In the only clinical trial that investigated the use of a hypnosedative drug in an "as-needed" regimen, zolpidem produced a global improvement in sleep (61,62). Zaleplon has an ultrashort half-life of about 1 hour, and has been shown in a number of studies to promote sleep initiation, but less so in promoting sleep maintenance. The adverse effects of zaleplon have also been shown to resolve more rapidly or be of a lesser in magnitude than those associated with benzodiazepines (including triazolam) and the longer acting nonbenzodiazepine hypnotics (zolpidem and zopiclone) (59).

Sedating antidepressants (e.g., amitriptyline, trazodone, mirtazapine), although not hypnotics per se, may be useful in the management of patients in whom depression and insomnia coexist. However, there is very little data regarding their effectiveness and safety in chronic insomnia. All antidepressants have potentially significant side effects, and this raises concerns regarding the risk:benefit ratio. Due to its sedating property, trazodone is currently the second most commonly prescribed agent in the United States, but according to a recent review, there is a lack of studies to show its effectiveness in patients with insomnia (63). Side effects such as dizziness, sedation, and psychomotor impairment raise concerns about its use, especially in the elderly.

Antihistamines, such as diphenhydramine or doxylamine, are also used to treat insomnia, as they make people feel sleepy. It is important to emphasize that these drugs do not improve sleep and are not helpful in the management of chronic insomnia. Furthermore, their use may result in decreased alertness, daytime sedation on the day following use, dizziness, dry mouth, constipation, and blurred vision. A number of other sedating medications (including barbiturates and antipsychotics) as well as several over-the-counter medications and herbal remedies (valerian) and other alternative therapies (e.g., L-tryptophan) have been used to treat insomnia, but data demonstrating the effectiveness and safety of these substances is lacking or only minimal. The potential risks, side effects, and toxicity of these various therapies should also be considered and their use in the treatment of chronic insomnia cannot be recommended (33).

Melatonin is the product of the pineal gland, and its disturbed metabolism is suggested to play a role in the mechanism of sleep disorders. Data regarding the efficacy and safety of melatonin are minimal. Studies have shown that melatonin and melatonin agonists regulate circadian sleep rhythms, and recent studies with a melatonin agonist have also demonstrated an effective hypnotic profile of the drug (64). Melatonin almost certainly will have a significant role as a chronotherapeutic agent.

Extra care and caution has to be exercised when treating insomnia in patients with renal impairment. Most hypnotics should be administered in appropriately

reduced doses, and interactions with the numerous medications used in the different CKD populations should be considered carefully when prescribing a hypnotic to patients with renal failure. Surprisingly, there is an almost complete lack of pharmacologic studies in renal patients suffering from insomnia. In a small randomized study using the PSQI, Sabbatini et al. (65). suggested that zaleplon improved sleep efficacy in maintenance hemodialysis patients. There are only a limited number of small studies available regarding nonpharmacologic approaches, including acupressure, to improve sleep in renal patients (66). Consequently, as suggested earlier, treatment suggestions can only be based on inferences from results obtained in various non-CKD populations.

Conclusion

Although sleep problems and sleep disorders (especially insomnia, RLS, and SAS) are frequent complaints in renal patients, there is an almost complete lack of well-designed studies assessing different therapies in this patient population.

This review focused on insomnia, which impairs daytime functioning, cognitive functioning, and memory, and possibly contributes to depressed mood and anxiety. Insomnia is associated with impaired quality of life and increased health care utilization in the general population. Nonpharmacologic methods such as behavioral techniques and cognitive therapy, as well as pharmacologic approaches and combinations of these methods should be used for the treatment of insomnia. There is a burning need for studies assessing the effect of long-term therapies of chronic insomnia both in the general population and in medically ill patients, including renal patients.

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