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## Sleep in Patients with ESRD Undergoing Hemodialysis

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### 1. Introduction

Sleep has been identified as an essential human need; this is partly because of the metabolic activities that occur while the individual is sleeping. Normal sleep is divided into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep comprises 75% to 80% of total sleep time (TST), and is characterized by relatively quiescent brain activity and decreased metabolic rate (Carskadon & Dement, 2000). NREM sleep consists of four stages (S1-S4), with each stage leading to a progressively deeper sleep. REM sleep follows slow wave sleep (SWS), or deep sleep, and increases over the night, comprising 20% to 25% of TST. REM sleep is characterized by an activated EEG pattern, muscle atonia, and episodic bursts of rapid eye movements. Normal sleep provides a period of physiologic and mental rest. During sleep, sympathetic tone decreases and parasympathetic tone increases, leading to a reduction in heart rate, arterial blood pressure, and cardiac output (Rosenthal, 1998). Deep sleep is theorized to be necessary for physiologic restoration. REM sleep is associated with dreaming, and is essential for maintaining emotional and cognitive well-being (Redline et al., 2004).

Waking and consciousness depend on the activity, of neurons in the ascending reticular activating system of the brainstem. These neurons project into the thalamus, hypothalamus and basal forebrain and eventually send projections to the cortex. There are particular neurotransmitters, such as the catecholamines, acetylcholine, histamine, glutamate and aspartate, that are localized within the reticular formation and have important roles in cortical activation and arousal (Jones, 1989). Sleep-promoting neurotransmitters include gamma aminobutyric acid (GABA), adenosine, and melatonin. Specific stages of sleep are regulated by the turning "on" and "off" of various neurons. REM "on" cells use GABA, acetylcholine, and glutamine, whereas REM "off" cells use norepinephrine and serotonin. "REM On cells" are cholinergic cells in the lateral pontine and medial medullary reticular areas that innervate the thalamus, hippocampus and hypothalamus. These cells discharge at high rates during REM and show little or no activity during NREM. "REM Off cells" are noradrenergic and serotonergic cells found in the locus coeruleus and raphe. These are cells which are slow or silent during REM sleep. Affecting levels of norepinephrine or serotonin can have an effect on REM sleep (Hoyt, 2005).

Sleep regulation is a balance between a homeostatic sleep need and an intrinsic body clock, or circadian pacemaker. Located in the suprachiasmatic nucleus, the circadian pacemaker determines the onset and termination of sleep, and is partially regulated by environmental

cues such as light and ambient temperature (Rosenthal, 1998). Melatonin, a physiologic sleep promoter, is inhibited by ambient light, and its circulation is decreased during daylight hours. The adrenal secretion of cortisol, which is associated with wakefulness, follows a circadian pattern. Regulated by the hypothalamic-pituitary axis, cortisol levels peak in the early morning hours in preparation for the increased metabolic demands during wakefulness (Mahowald, & Schenk, 1989).

Some medical illnesses, such as congestive heart failure (CHF), diabetes mellitus, chronic obstructive pulmonary disease and renal disease, can directly impair sleep physiology, leading to a cyclical interaction (Ballard, 2005). End-stage renal disease (ESRD) is one of these diseases. Approximately 50% of patients with chronic end-stage renal disease undergoing hemodialysis (HD) have insomnia and other sleep disorders (Hanly, 2007). Patients often complain of restless leg syndrome (RLS), periodic limb movement disorder (PLMD), bone pain, nausea, and pruritus (Merlino et al., 2006). The etiology of sleep disorders appears to be related to metabolic derangements associated with ESRD or from coexisting diabetes mellitus (Ballard, 2005).

## **2. Sleep problems in hemodialysis patients**

Sleep complaints and sleep disorders are common in patients with end-stage renal disease. Although variable, their prevalence has been reported to be higher when compared to the general population (Merlino et al., 2006). The experiences of sleep alteration in ESRD patients have been studied. Interestingly, 80% of hemodialysis patients suffer from sleep abnormalities and the prevalence is higher than that in the general population (Gul et al., 2006). Holley et al. (1992) surveyed 70 dialysis patients, and reported sleep disturbance experienced mainly included trouble falling asleep (67%), nighttime waking (80%), early morning waking (72%), restless legs (83%), and jerking legs (28%). However, Walker et al. (1995) found daytime sleepiness was the most commonly reported problem (66.7%) followed by restless legs syndrome (57.4%). Generally, the most prominent sleep disorders among hemodialysis patients are sleep apnea syndrome, restless leg syndrome, periodic limb movement disorders, and insomnia (De Santo et al., 2005; Holley et al., 1992; Sabry et al., 2010).

### **2.1 Sleep apnea syndrome**

The prevalence of sleep apnea syndrome in hemodialysis patients is at least 10 times higher (Kraus & Hamburger, 1997) than those values reported in the general population (Young et al., 1993). In another recent investigation, an apnea/hypopnea index higher than 5 was found in 31% of the (young) non-diabetic HD patients studied (Rodriquez et al, 2005).

Sleep apnea syndrome (SAS) is a major clinical disturbance defined as an intermittent interruption of air flow at the level of nose and mouth during sleep. These abnormalities cause frequent decreases in O<sub>2</sub> saturation and awakenings. Episodes of apnea are considered clinically significant if they persist for more than 10 s; however, apnea episodes may last up to 2 min. SAS is the clinical consequence of frequent (at least 10 events per hour) episodes of apnea during sleep (Tatomir et al., 2007). There are three major types of sleep apnea: obstructive sleep apnea (OSA), the central type (CSA), and the mixed type, which includes features of both obstructive and central apnea. OSA is characterized by obstruction of the air flow determined by the occlusion of the oropharyngeal tract (Zoccali et al., 2001).

OSA occurs when the patient no longer has airflow but there is respiratory effort. CSA is determined by the transient abolition of nerve conduction to the respiratory muscles. Central apnea is defined when the patient has both cessation of airflow and the lack of respiratory effort followed by spontaneous resumption of breathing. Mixed apnea is the combination of central and obstructive apneas. All of these conditions can cause arterial oxygen desaturation and they may even be present in the same person (Tatomir et al., 2007; Zoccali et al., 2001). Researchers have speculated that the chronic metabolic acidosis suffered by patients with hemodialysis causes these sleep disorders; as the body attempts to correct the acidosis, the patient exhales more carbon dioxide and the hypocapnia that results may be inadequate to fuel respiration (Kimmel, 1989). Another theory is that these patients frequently have peripheral neuropathy, either from the ESRD or diabetes mellitus, and if the neuropathy affects the nerves innervating the upper airway, then SAS will occur (Fletcher, 1993). There is also evidence that SAS is associated with increased morbidity, and mortality, as the patient with ESRD who suffers with SAS is looking at a future with probable pulmonary hypertension and right heart failure, as well as a shortened lifespan (Fletcher, 1993; Parker, 1997). While, there are no ready answers for the causes of these sleep disorders seen in patients with ESRD undergoing HD, it is crucial that the health care provider be aware of the syndrome.

The awareness of SAS as a potent cardiovascular risk factor in ESRD undergoing HD has generated new enthusiasm in examining novel therapeutic strategies to modify sleep apnea in the patient population. To date, conservative non-pharmacological treatments (e.g. weight loss and avoidance of potentiating medications) have yielded limited success. Nasal continuous positive airway pressure therapy remains a mainstay of treatment of SAS in the non-ESRD population. Continuous positive airway pressure involves a mask fitting over the nose or mouth in which positive pressure is administered to the airway keeping the upper airway patent during sleep. In the general population, the treatment of sleep apnea with continuous positive airway pressure improves quality of life (D'Ambrosio et al., 1999), vigilance, cognition, sexual performance, and normalizes nocturnal blood pressure profile (Faccenda et al., 2001). In the HD population, continuous positive airway pressure was used in a small study of eight patients with some improvement in nocturnal oxygenation, and five of six patients reporting improved daytime alertness (Pressman, 1993). Finally, given the contribution of uremia in the pathogenesis of SAS in ESRD, attempts in optimizing uremia control in the forms of nocturnal hemodialysis (NHD) and renal transplantation have shown early clinical success (Auckley et al, 1999; Hanly & Pierratos, 2001). It is tempting to speculate that similar to those with refractory hypertension, the treatment of sleep apnea in the HD population would improve their quality of life, augment rehabilitation, and perhaps impact on the poor survival of patients.

## 2.2 Restless Legs Syndrome

Restless Legs Syndrome (RLS) is a neurological movement disorder that is common, under-diagnosed, under-treated, and has a poorly understood etiology (Patrick, 2007). Restless legs syndrome (RLS) is a sensorimotor movement disorder characterized by the irresistible need to move associated with feelings of discomfort and paresthesias (International Restless Legs Syndrome Study Group, 2003). The incidence of idiopathic RLS (iRLS) varies between 5–15% in the general population (Nicholas et al., 2003). In the HD population, the prevalence of secondary RLS may be greater, reported to be between 6–62% (Takaki et al., 2003; Unruh et al., 2004) with some geographic variability (Kavanagh et al., 2004). With employment of

standardized criteria by IRLSSG, this decreased to 12–48% (Siddiqui et al., 2005; Takaki et al., 2003; Unruh et al., 2004). RLS is observed more commonly in women than men, more commonly with increasing age and with co-morbid diabetes. Other potential correlates of RLS include lower socio-economic status, worse somatic and mental health and diabetes (Berger et al., 2004; Siddiqui et al., 2005). A high correlation between RLS and PLMS has also been noted (Allen et al. 2003, Liao et al., 2008).

The pathophysiology of RLS in uremia remains unknown however, several theories have been proposed. Potential risk factors include anemia, iron deficiency, dialysis vintage, calcium/phosphate imbalance, and peripheral and central nervous system abnormalities (Berger et al., 2004; Unruh et al., 2004).

Evidence for a possible relationship of iron deficiency to RLS in this patient population has been explained by the universal occurrence of anemia, which is commonly acquired in patients with end-stage renal disease due to inadequate production of erythropoietin (Gigli et al., 2004). Anemia in ESRD is associated with several co-morbid conditions, including congestive heart failure, stroke, cognitive dysfunction, left ventricular hypertrophy, and worsening iron deficiency due to loss from hemodialysis (Allen, 2004; Gigli et al., 2004). Ferritin levels under 100 ng/mL reflect depletion of iron stores and complicate the treatment of anemia in patients on dialysis (Easom, 2006; Patrick, 2007).

Multiple causes of secondary RLS including iron deficiency anemia, diabetes mellitus, Parkinsons disease, pregnancy, rheumatic disease, venous insufficiency and less commonly in association with peripheral neuropathies, vitamin deficiencies, lumbosacral radiculopathy, spinal stenosis, excess caffeine intake, administration of some tricyclic antidepressants, hypoglycemia and hypothyroidism (Nichols et al., 2003; Siddiqui et al., 2005; Unruh et al., 2004). The revised IRLSSG criteria (Allen et al. 2003) for RLS included four essential diagnostic criteria additional supportive features. The criteria include unpleasant and uncomfortable sensations associated with an urge to move the limbs with symptoms worsened by rest, relieved by activity and typically worse toward the evening. Positive family history, initial therapeutic response to L-dopa or a dopamine-receptor agonist are supportive evidence. At least 85% of patients with RLS may also have concomitant periodic limb movements (PLMS) though this may be the result of other disorders such as obstructive sleep apnea.

Treatment of ESRD-associated anemia with erythropoietin has been shown to decrease arousal due to PLMS and produce trends toward higher sleep quality (Benz et al 2000). As will be reviewed later, intravenous (I.V.) iron in ESRD patients has been shown to be highly effective in causing remission of RLS symptoms (Sloand et al., 2004).

Given that alterations of the dopaminergic pathways may contribute to the development of RLS in ESRD, pharmacological treatment of RLS with Levodopa (L-DOPA) has been studied and was shown to improve sleep and reduce nocturnal limb movements in three prospective trials (Sandyk et al. 1987; Trenkwalder et al., 1995; Walker, 1996). Recently, treatment with pergolide, a dopamine agonist was also examined in a double-blind placebo-controlled crossover study in ESRD patients (Pieta et al., 1998). In contrast to the use of L-DOPA, pergolide resulted in decreased symptoms without objective improvements in nocturnal limb movement or sleep architecture. Limited beneficial data regarding the use of other dopamine agonists have also been reported (Miranda et al., 2004; Pellecchia et al., 2004). Folate is also involved in the production of dopamine in the CNS. Folate, as 5-methyltetrahydrofolate, increases production of CNS tetrahydrobiopterin, a cofactor in tyrosine hydroxylase production significant reduction in RLS symptoms and decreased leg movements during sleep ( $p=0.018$ ). With the exception of this one trial, there is only limited

information from case reports of significant symptom reduction in pediatric RLS using dopaminergic agents (Konofal et al., 2005)

### 2.3 Periodic Limb Movement Disorder

Periodic limb movement disorder (PLMD) is a condition characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur either during sleep (PLMS) or in wakefulness (PLMW) (Walker et al., 1995). This syndrome is more often seen in the patient with ESRD than in the general population (Pressman et al., 1995). The presence of PLMS is responsible for sleep problems in up to 72% of patients with ESRD (Benz et al., 2000) and the presence of PLMS is a more accurate predictor of mortality than coexisting diseases, serum albumin, or urea reduction ratio (Winkelman et al., 1996). A high correlation between RLS and PLMS has also been noted (Allen et al. 2003).

Treatments with high-dose iron dextran and normalization of hematocrit with recombinant human erythropoietin have been demonstrated to improve RLPLMD in ESRD patients (Benz et al, 1999; Sloand et al., 2004). Alterations in dopamine and opioid synthesis may also play a role in the high prevalence of RLS and PLMD in uremia; however, data are limited. Indirect evidence stems from the notion that treatment with dopamine agonists, dopamine precursors in ESRD patients may improve RLS and PLMD symptoms (Sandyk et al. 1987; Trenkwalder et al., 1995; Walker, 1996).

### 2.4 Insomnia

Insomnia is defined as a disorder of difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), and/or early morning awakening (EMA). Insomnia is commonly defined as the subjective sensation of short, unsatisfying sleep, despite the ability to sleep (Sabbatini et al., 2002). It may be secondary either to trouble falling asleep and/or to night-time waking, which must be persistently present (i.e. three to four times a week for several weeks) (Leger et al., 2002). The prevalence estimates of insomnia vary because of differences in definition, diagnosis, population characteristics, and research methodologies. Insomnia is a common sleep problem, however, and its prevalence in the general population ranges from 4% to 64% (Terzano et al., 2004; Chesson et al., 2000). The prevalence of insomnia is substantially greater in dialysis patients and has been reported to range from 45% to 59% (Îliescu et al., 2003; Îliescu et al., 2004; Sabbatini et al., 2002).

Insomnia is characterized by one or more of the following symptoms: difficulty falling asleep ("sleep onset insomnia"), difficulty staying asleep ("sleep maintenance insomnia"), early awakening or poor sleep quality ("non-restorative sleep") (Ohayon et al., 2002; Meyer, 1998). 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 (SASRLSPLMS) are suspected (Bonner et al., 2008).

Insomnia may be caused by a variety of reasons, with the most frequent causes listed by researchers as: restless legs syndrome (RLS), periodic leg movements during sleep (PLMS), sleep apnea syndrome (SAS) and depression (Kimmel, 1989; Parker, 1997; Welch & Austin, 2001). The prevalence of insomnia due to RLS in dialysis patients ranges from 57% to 83% (Holley et al., 1992; Sabbatini et al., 2002; Walker et al., 1995). Elderly patients, those with longer dialysis durations, dialysis shift, and those with high levels of parathyroid hormone (PTH) or diabetes mellitus are at higher risk of insomnia; however, the dialysis type and biochemical parameters are not important determinants of insomnia (Han et al., 2002; Sabbatini et al., 2002).

Most studies assessing the effectiveness of different treatment modalities in insomniacs address short-term treatment of insomnia (Montgomery & Dennis., 2004; Morgan et al., 2003; Smith et al., 2002). 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 HD populations should be considered carefully when prescribing a hypnotic to patients with renal failure (Novak et al., 2006). 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. (2003). suggested that zaleplon improved sleep efficacy in maintenance hemodialysis patients.

Nonpharmacologic interventions include sleep hygiene measures relaxation therapy and biofeedback stimulus control therapy sleep restriction and cognitive behavioral therapy (Montgomery & Dennis., 2004; Morgan et al., 2003). These interventions have been shown to be beneficial in the long-term management of patients with chronic hypnotic use. 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.

### **3. Related factors with sleep problems in hemodialysis patients**

A multitude of causes including anemia, blood urea levels, plasma creatinine levels, parathyroid hormone (PTH) concentrations, increased blood pressure, quality of life, and illness intrusiveness may contribute to sleep disturbances in patients on maintenance hemodialysis (Hanly et al., 2003; Iliescu et al., 2004; Sabbatini et al., 2003). Furthermore, there is a positive correlation between sleep disturbances and increased morbidity and mortality related to cardiovascular disease and infectious complications, the 2 major causes of death in hemodialysis patients (De Santo et al., 2005). Sleep disorders in hemodialysis patients is a multifactorial complaint, stemming from Uremic toxins and dialysis procedure, other medical problems, psychiatric or psychosocial background.

#### **3.1 Uremic toxins**

Several studies in the past 30 years have shown that uremic patients are at great risk for disordered sleep. A study by Millman et al. (1985) noticed a slight but significant relationship between sleep apnea syndrome and azotemia. In a recent prospective study of incident HD patients followed-up for 1 year, higher dialysis efficiency was associated with fewer sleep disturbances (Unruh et al., 2006). These latter data are further supported by the results of Hanly et al. (2001), who studied patients on conventional hemodialysis (4 h three times a week) who then switched to nocturnal (intensive) dialysis (8 h for 6 or 7 days/week). A spectacular correction of sleep apnea was recorded in this small-scale study (Hanly et al., 2001). Finally, the impact of uremic toxins is highlighted by the fact that sleep disorders are more frequent and more severe in dialyzed patients compared with subjects with pre-dialysis CKD (Merlino et al., 2006).

#### **3.2 Interdialytic weight gain and hypertension**

Excessive interdialytic weight gain has been associated with poor compliance and high blood pressure (Rahman et al., 2000). While the mechanism of the association between

interdialytic weight gain and sleep problems is unclear, we speculate that large interdialytic weight gains result in expanded intravascular volume, which has been associated with upper airway obstruction (Chiu et al., 2006).

The length of sleep during the night before a hemodialysis session after a long interdialytic interval (3 days, the “weekend interval”) is significantly shorter compared to the usual sleep length following a short interdialytic interval. This led to some speculation regarding the possible effect of interdialytic weight gain (IWG) on sleep (Bertini et al., 1999). Furthermore, patients with uncontrolled pre-dialysis systolic pressure (usually a sign of hypervolemia in these patients) experience clinically overt insomnia more frequently (De Santo et al., 2001); in patients with chronic diseases, systolic hypertension appears to be a cause of sleep disturbances (Katz & McHorney 1998; Sabbatini et al., 2002; Thase, 2005).

### **3.3 Dialysis shift**

The dialysis shift has several effects on patients with ESRD. Morning-shift HD patients experience more insomnia (Sabbatini et al., 2002), but also have longer survival times (Bliwise., 2001) than patients on other dialysis shifts. In according to another study (Merlino et al., 2006), for patients undergoing HD in the morning shift, the risk of subclinical insomnia is up to 18 times higher than for those who have their dialysis session in the afternoon. However, morning-shift HD patients have higher intradialytic sleepiness, which is associated with more decreased body temperature during HD, than patients on other dialysis shifts (Parker et al., 2003).

### **3.4 Dialysis vintage**

The longer the dialysis vintage, the more significant is the prevalence of sleep quality disorders (Veiga et al., 1997). In a study by De Santo et al., (2005), patients with subclinical or clinical sleep disorders had double the dialysis vintage of those without sleep complaints; in patients with a medium dialytic age of 75 months, the prevalence of sleep disorders is close to 80%. These data are not surprising, taking into account the accumulation of comorbidities, including peripheral neuropathy and CVD, whilst on dialysis on long-term. In a polysomnographic study by Tatomir et al.,(2007) in patients hemodialyzed for more than 10 years, all patients has disturbed sleep with frequent awakening and reduced sleep efficiency. One-half of these patients had sleep-related breathing disorders, i.e. sleep apnea syndrome.

### **3.5 Restless legs syndrome**

Restless legs syndrome (RLS) usually becomes apparent during resting and may significantly interfere with sleep. An association between RLS and insomnia in patients on maintenance hemodialysis has been suggested already by a few papers (Musci et al., 2005; Sabbatini et al., 2002; Walker et al., 1995). Moreover, RLS is associated with a low quality of sleep and lower quality of life.

### **3.6 Other medical factors**

Other medical factors include the pain and discomfort caused by illnesses such as arthritis, cardiovascular disease, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, neurological disorders, asthma, headaches, and more. The prognosis of patients with chronic uremia is influenced by the presence of comorbidities, mainly by

cardiovascular disease (CVD), which causes roughly 50% of deaths (Covic et al., 2006). A study by Mucsi et al. (2004), demonstrated that comorbidities are independent predictors of sleep disturbances in patients on maintenance dialysis. According to another study, the average Charlson Comorbidity Index (CCI) in patients without sleep disorders was 4.10, while scores in patients with subclinical and clinically overt sleep disorders were 6.10 and 6.81, respectively (De Santo et al., 2005). This highly significant association in the Italian HD population was maintained regardless of age. To conclude so far, any in-depth research on the quality of sleep in renal patients must consider the magnitude of comorbidities.

### 3.7 Age

Sleep difficulties are closely correlated with older age in patients with chronic uremia (Iliescu et al., 2003). Yoshioka et al. (1993) found that advanced age and long-term dialysis therapy directly affected patients experiencing sleep problems. The disorders are similar to those described in the general population, where the prevalence and severity of sleep disorders are also associated with old age. Each decade of age increases the risk of insomnia by 239%, and the risk of overt clinical insomnia by 51% (De Santo et al., 2005). Mollaoğlu (2004) reported a negative correlation between age and sleep quality, with sleep quality decreasing with advanced age in their study of 105 HD patients. In addition, community-based studies have shown that sleep quality could be deteriorated in elderly patients due to increased frequency of physical diseases, multiple drug use, primary sleep disturbances, or lifestyle modifications (Brandenberger et al., 2003; Kamel & Gammack 2006).

### 3.8 Depression

The psychiatric condition most commonly causing sleep disorders is depression that may affect up to 50% of this patient population (Covic et al., 2006). The relationship between depression and sleep disorders is well known both in the general population and in patients undergoing hemodialysis (Iliescu et al., 2003). Depression can be a cause, as well as a result, of insomnia. Dialysis patients with a Pittsburgh Quality Index Sleep score of >5 (patients with a “difficult sleep”) have a prevalence of overt depression of 20%, while among ESRD patients reporting a normal sleep, the prevalence of depression is almost nil (Iliescu et al., 2003).

### 3.9 Medications and other substances

Medications and other substances which may cause insomnia include beta-blockers, bronchodilators, corticosteroids, CNS stimulants, Tagamet, cardiovascular drugs, neurological drugs, alcohol, caffeine and nicotine (Merlino et al., 2006; Rosenthal, 1998; Unruh et al., 2006). Most prescribed as well as over-the-counter medications produce side effects which are either sedating or stimulating. Drugs which cause daytime sleepiness include analgesics, benzodiazepines and antihistamines (Rosenthal, 1998; Unruh et al., 2006). According to recent investigations, the use of hypnotic medication in dialysis patients is rather modest: 8–10% (De Santo et al., 2005; De Santo et al., 2001). In a large study, the reported use of sleep-inducing medication was even lower—3.6% (Merlino et al., 2006). However, dialysis patients with severe sleep disorders use specific medication more frequently (24%) (De Santo et al., 2005). Improved hemodialysis techniques, socio-economical disparities in the studied populations, and reluctance by nephrologists to prescribe psychotropic medication may explain these disparities. However, we must be aware that chronic auto-administration of hypnotic medication may be more frequent in

ESRD patients compared to the general population. Moreover, according to recent data from the CHOICE incident dialysis population, use of benzodiazepines is associated with altered sleep quality during the first year of dialysis. Although this study was unable to distinguish between cause and effect, more effective dialysis and cognitive behavioral therapy have been suggested in patients with sleep disorders in need of sleep-inducing medication (Unruh et al., 2006). Moreover, many antidepressants actually cause paradoxical restlessness, therefore systematic administration of these drugs should be subjected to close clinical follow-up, which should be easy to accomplish in hemodialysis patients.

Alcohol is widely used as a sleep aid. Although it does shorten sleep latency, it also causes sleep fragmentation, decreased REM, REM rebound and early morning awakenings. The use of alcohol combined with hypnotics may exacerbate sleep difficulties even more (Rosenthal, 1998). Alcohol and (particularly) tobacco abuse is highly associated with increased prevalence of sleep disorders in ESRD (Merlino et al., 2006). Caffeine and other stimulants such as nicotine have been shown to increase sleep latency and sleep fragmentation, and to decrease total sleep time (Rosenthal, 1998). Current smoking is also related with decreases in sleep quality during the first year of dialysis therapy in incident patients (Unruh et al., 2006). Caffeine intake appears to have no significant impact on insomnia in ESRD (Sabbatini et al., 2002).

#### **4. Sleep quality and evaluation of sleep in hemodialysis patients**

Sleep quality is an important clinical construct for two major reasons. First, complaints about sleep quality are common; epidemiological surveys indicate that 15-35 % of the adult population complain of frequent sleep quality disturbance, such as difficulty falling asleep or difficulty maintaining sleep. Second, poor sleep quality can be an important symptom of many sleep and medical disorders (Buysse et al., 1989).

Sleep quality" is sometimes used to refer to a collection of sleep measures including total sleep time (TST), sleep onset latency (SOL), degree of fragmentation, total wake time, sleep efficiency, and sometimes sleep disruptive events such as spontaneous arousals or apnea. The widely employed Pittsburgh Sleep Quality Index (PSQI), for example, provides a measure of global sleep quality based on a respondent's retrospective appraisal (past month) of an array of sleep measures, including sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (Krystal & Edinger, 2008). Sleep quality is also sometimes inferred from a collection of objective indices taken from polysomnography (PSG). PSG is the most valid and accurate way to assess sleep. Measures derived from PSG include: (a) total sleep time, (b) sleep efficiency (ratio of time spent asleep/time in bed), (c) sleep latency (time to fall asleep after lights out), (d) amount of wake time during sleep periods (waking after sleep onset, WASO), (e) number of awakenings, and (f) amount of each sleep stage ( Landis al., 2002).

Among these objective indices are measures such as sleep onset latency, total sleep time, wake time after sleep onset, sleep efficiency, and number of awakenings that correspond to like measures taken from various available self-report instruments (e.g., sleep diaries, PSQI, etc.) (Buysse et al., 2006). However, PSG also provides a number of measures that reflect the architecture of sleep such as the percentage or temporal amounts of stage 1 sleep, stage 2 sleep, slow wave sleep or rapid eye movement (REM) sleep. Despite having no self-report analogues, these latter measures also have been employed by some as indices of sleep quality (Krystal & Edinger, 2008).

Most of the recent studies on quality of sleep use different questionnaires assessing various aspects of sleep. The Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, and the Berlin Questionnaire are most frequently applied. Results derived from these questionnaires are limited by the subjective perception/sincerity of the patients, and thus are an imperfect substitute for more objective research methods on sleep in patients with chronic uremia (Chen et al, 2006; Iliescu et al., 2003; Mollaoglu & Mollaoglu, 2009; Sabbatini et al., 2003).

Researchers have documented that ESRD patients reported significantly poorer subjective quality of sleep in comparison to the general population (Holley et al., 1992; Parker, 2005). The reported prevalence of 'poor sleep', including sleep-wake complaints, sleep-disordered breathing and excessive sleepiness, in dialysis patients is in the range of 45–80% (Afshar et al., 2011; Parker, 1996; Walker et al., 1995; Wei et al., 2011 ). In a another study It was examined the quality of sleep in 89 subjects with ESRD on haemodialysis using the PSQI and found a prevalence of 'poor sleep' (global PSQI>5) of 71% (Iliescu et al., 2003). Also, decreased quality of sleep is common in dialysis patients and is associated with decreased health-related quality of life (Iliescu et al., 2003; Williams et al., 2002).

The complex evaluation of sleep in patients with renal disease may be accomplished only by means of polysomnography. Polysomnography includes the comprehensive evaluation of the patient during sleep by electroencephalography, electrooculography, myography, quantification of respiratory efforts (by plethysmography), pulseoxymetry and noninvasive evaluation of CO<sub>2</sub> blood level, and heart rate measuring (Tatomir et al., 2007). Parker et al. (2003) examined by polysomnography 16 patients with HD and 8 patients with pre-dialysis CKD. Dialysis patients, in comparison with non-dialyzed CKD subjects, have a shorter sleep time. The REM phase is also shortened, time until falling asleep is longer, and respiratory events are more frequent. The sleep latency period was double in renal patients without dialysis compared to those with dialysis. Moreover, the prevalence and severity of periodical limb movement is higher in dialysis patients, as well as the number of short-term awakening periods (Parker et al., 2003). The authors suggest that sleep disturbances may have a different etiology in dialyzed patients compared to pre-dialysis CKD subjects. Functional and psychological factors may play a more prominent role in the pre-dialysis group, whereas intrinsic sleep disruption (arousals, apneas and limb movements) secondary to intermittent daytime HD sessions may play a more prominent role in patients with chronic uremia. Taken as a whole, renal patients experience a significant reduction in sleep length and efficiency compared to the general population (Parker et al., 2005).

The studies have shown poor the quality of sleep in HD patients to be associated with female sex, older age, caffeine intake, recombinant erythropoietin therapy, pain, cardiovascular disease, physical functioning, larger body mass index (BMI), exercise, dialysis adequacy, parathyroid hormone, serum creatinine and quality of life (QOL) (Benz et al., 1999; Sabatini et al., 2002; Walker et al., 1995). Hanly et al. (2003) examined daytime sleepiness with multiple sleep latency tests in 24 haemodialysis patients and found strong correlation between sleep latency and BUN. In addition, psychological problems do represent crucial factors in influencing the quality of sleep in hemodialysis patients, as emphasized by all the previous studies in prevalent patients with renal disease, with depression playing a prominent role, followed by anxiety, sexual problems, financial strains, and isolation (Iliescu et al., 2003; Iliescu et al., 2004; Markou et al., 2006; Novak et al., 2006).

Considering the strict linkage between some of these factors affecting sleep and hemodialysis, it is tempting to speculate that treating sleep problems, while improving the overall quality of life, might positively affect hemodialysis. In addition, with this point of

view, psychological, behavioural and pharmacologic interventions that promote sleep will represent a more than promising area for future research in hemodialysis patients.

The above studies results show that the sleep characteristics of hemodialysis patients need to be routinely evaluated. In addition to medical treatment to eliminate the sleep problems of hemodialysis patients and increase their sleep quality, the implementation of sleep hygiene interventions that can play a part in the regularity of patients' sleep could also be beneficial. These interventions would include an environment with a comfortable room temperature and ventilation, minimal noise, a comfortable bed, and proper lighting. These interventions should apply to each patient's personal routines (Mollaoglu & Mollaoglu, 2009).

## 5. Management of sleep problems in hemodialysis patients

Proper management of sleep problems in ESRD patients requires in the first instance a proper identification of sleep abnormalities (extensively discussed above). Although significant research has been done to characterize sleep abnormalities in hemodialysis patients (Holey et al., 1992; De Santo et al., 2005; Merlino et al., 2006), little has been published regarding proper treatment. In the absence of guidelines, nephrologists rely largely on some published data and on opinion-based medicine. Sleep problems lower quality of life and contribute to physical and mental health problems. Sleep disorders and lack of sleep are an under treated threat to the public health. Sleep professionals have recognized the behavioral components of sleep disorders for decades, yet most patients never get a proper diagnosis and treatment (Mollaoglu & Mollaoğlu, 2009).

Periodic clinical assessment of sleep complaints should become routine for dialysis staff. Early identification of sleep problems and interventions to improve sleep quality is essential, because sleep disturbance that persists for a long period of time could decrease general health and functioning (Sabbatini et al., 2003; Tatomir et al., 2007). Increasing evidence supports the effectiveness of both pharmacologic and nonpharmacologic therapies for sleep problems (Edinger et al., 2001; Montgomery & Dennis, 2004; Smith et al., 2002). Pharmacologic therapy are discussed in the sleep disorders section.

The most effective nonpharmacologic interventions tested to date include all or most of the following components: *sleep hygiene instruction, sleep restriction, stimulus control, relaxation training, and cognitive modification* (Edinger et al., 2001; Montgomery & Dennis, 2004).

### 5.1 Sleep hygiene

Sleep hygiene involves basic education on how the sleep environment, caffeine, alcohol, nicotine, food and exercise affect sleep (Smith et al., 2002). Sleep Hygiene is an educational approach designed to teach insomnia patients as well as the population at large how to maintain healthy behavioral habits which promote better sleep. It is important to understand that successful treatment is only possible if the patient complies with suggestions to improve sleep hygiene (Edinger et al., 2001). Below are summarized tips for sleep hygiene

#### *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 nap 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, ear plugs or a white noise machine if necessary. A cooler room is recommended. Use a humidifier if the air is too dry.

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 (Morin et al., 1999). Building a regular sleep schedule and creating an appropriate sleeping environment as well as regular physical activity are very important in combating insomnia or insomnia-like presentations in RLS/PLMD (Montgomery & Dennis, 2004).

In terms of sleep hygiene for RLS/PLMD, there are two main points that bear highlighting. First, the avoidance of alcohol, caffeine and nicotine may be underscored because of their potential contribution to RLS symptoms and/or PLMs. Second, other sleep hygiene practices may or may not have any utility for patients with RLS. Particularly when sleep hygiene is provided to patients as a handout or pamphlet, there is no indication that this helps promote sleep in any patient group. (Martin, 2000; Pigeon & Yurcheshen, 2009).

## 5.2 Relaxation and biofeedback techniques

Relaxation and biofeedback techniques for treating insomnia are based on the assumption that insomnia patients are overly aroused and anxious, and this interferes with their ability to initiate and/or maintain sleep (Lacks, 1993). Relaxation techniques are designed simply to teach patients to relax, and thus improve their ability to sleep. Of several relaxation methods, none has been shown to be more efficacious than the others. Progressive muscle relaxation, autogenic training and electromyographic biofeedback seek to reduce somatic arousal (e.g., muscle tension), whereas attention-focusing procedures such as imagery training and meditation are intended to lower presleep cognitive arousal (e.g., intrusive thoughts, racing mind) (Spielman et al., 1987).

In general, biofeedback training is an effective treatment for some insomnia patients, and is as effective as other non-pharmacologic interventions (Morin et al., 1999). If patients can train themselves to relax before sleep or at night after an awakening, they are more capable of falling asleep and staying asleep. It is believed that the beneficial effects of these methods extend beyond the sleep problems in that they facilitate better coping skills in general (Martin, 2000).

Structured exercise programs may also improve symptoms of insomnia (Montgomery & Dennis., 2004). 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 (Novak et al., 2006).

### 5.3 Stimulus-control therapy

Stimulus-control therapy is a behavioral approach based on the premise that some sleep disturbances are behaviorally conditioned, so that the patient associates the bedroom environment with arousal. The main objective of stimulus control therapy is to reassociate the bed and bedroom with the rapid onset of sleep.

Below are summarized instructions for stimulus-control therapy (Martin, 2000).

#### *Instructions for Stimulus-Control Therapy*

- Patient goes to bed only when sleepy.
- If not asleep within about 10 minutes, patient gets out of bed, and does not return to bed until sleepy.
- When patient returns to bed, if not asleep within 15 minutes, gets out of bed.
- Pattern is repeated until patient can fall asleep within a few minutes.
- Must get up at the same time each morning (even if only slept 2 hours).
- Bed is used only for sleeping (not for watching television, reading exciting books, etc).
- All naps during the day must be avoided.

This method focuses primarily on shortening sleep onset, however, in the case of sleep maintenance insomnia, the instructions may be followed when the patient awakens and cannot fall back to sleep during the night. The patient should avoid lying awake in bed as much as possible and only go to bed when sleepy. No stimulating or distracting activities (e.g. reading exciting books or articles, watching television, looking at a clock) should be available. Although the patient cannot control sleep onset, wake up time should be fixed, so that a regular sleep/wake schedule will develop. Prohibiting daytime naps is important to take advantage of the sleep deficit accumulated since the sleep period on the previous night, which in itself can shorten sleep onset. As with all psychological therapies, compliance is enhanced when the instructions and their rationales are explained to the patient.

Stimulus control therapy has been shown to be effective in shortening sleep latency compared with placebo intervention in insomnia patients (Lacks, Bertelson, Gans & Kunkel, 1996). Clinical trials have documented the efficacy of stimulus control therapy for both sleep onset and sleep-maintenance insomnia (Espie et al., 1989; Lacks et al., 1993)

### 5.4 Sleep restriction therapy

Sleep restriction therapy, is based on the observation that many insomnia patients spend an excessive amount of time in bed in futile attempts to achieve more sleep (Spielman, Saskin, & Thorpy, 1987).. Sleep restriction therapy consists of curtailing the amount of time spent in bed to increase the percentage of time spent asleep. This improves the patient's sleep efficiency (time asleep/time in bed). For example, a person who reports staying in bed for eight hours but sleeping an average of five hours per night would initially be told to decrease the time spent in bed to five hours. The allowable time in bed per night is increased 15 to 30 minutes as sleep efficiency improves. Adjustments are made over a period of weeks

until an optimal sleep duration is achieved. Typically, it is best to alter the bedtime and to keep the rising time constant in order to maintain a regular sleep-wake rhythm. By creating a mild state of sleep deprivation, this therapy promotes more rapid sleep onset and more efficient sleep (Hauri, 2000). To minimize daytime sleepiness, time in bed should not be reduced to less than five hours per night. Sleep restriction therapy is modified in older adults by allowing a short afternoon nap.

Lichstein and Reidel (1994) concluded that sleep restriction therapy is actually the preferred technique for insomnia in older patients. In a later study they combined sleep restriction with sleep education for older insomnia patients, comparing a self-help technique (a guiding video) with therapist guidance (Riedel et al., 1995). While the self-help technique alone showed improvement on some sleep variables, therapist guidance was superior in that it improved sleep latency, wake time after sleep onset and sleep satisfaction.

Implementation of this technique requires a high level of motivation and compliance on the patient's part, and close follow up by the clinician. Below are listed the rules for sleep restriction therapy.

#### *Instructions for Sleep Restriction Therapy*

- Patient is only allowed to stay in bed for the amount of time they think they sleep each night, plus 15 minutes. For example, if patient reports sleeping only 5.75 hours, they are allowed to stay in bed for 6 hours.
- Patient must get up at the same time each day. If normal waking time is 6:30, patient is allowed to go to bed at 12:30.
- Napping is not allowed.
- When sleep efficiency has reached 85%, the patient can go to bed 15 minutes earlier.
- This procedure is repeated until the patient can sleep for the desired amount of time.

### **5.5 Weight loss**

Upper-body obesity is a risk factor for OSA, and it is well documented that weight loss has a notable ameliorative impact on the occurrence of OSA (Ancoli-Israel et al., 1996; Smith et al., 1985). Since OSA results from closure of the airway, excess fatty tissue in the neck area may be a contributing factor. This supports the notion that weight plays a significant role in the presence and severity of sleep disordered breathing although no conclusive treatment trials have been published at this time.

### **5.6 Light therapy**

The most influential treatment for circadian rhythm disturbances is increased exposure to bright light. This form of therapy, which directly targets the circadian system, is much preferred over hypnotics and other sedative medications. Since light is the most important synchronizer in our circadian system, increasing bright light exposure during certain times of the day can shift circadian rhythm phase and increase its amplitude. Specifically, bright light exposure in the evening causes a phase delay, while morning bright light exposure causes a phase advance in circadian rhythms, including rhythms of melatonin, core body temperature and sleepiness (Martin et al., 2000).

### **5.7 Cognitive-behavioral therapies**

Many behavioral sleep medicine interventions are based on cognitive-behavioral therapies (CBT). The focus is on systematically introducing behavioral changes that have been proven

to improve sleep. This could include changes in sleep schedule and changes in the contingencies and reinforcers that promote sleep. The cognitive approach focuses on looking internally to examine, manage, or modify sleep interfering thoughts and beliefs that can interfere with sleep. 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 (Montgomery & Dennis, 2004). 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 (Edinger & Sampson, 2003).

## 6. Conclusion

Considering that the most frequent sleep complaints, such as insomnia, OSAS and RLS, are related to a significant negative impact on functional health status in uraemic patients, the nephrologists should improve their recognition and treatment of these conditions to restore the quality of life of their patients. A good sleep history and, when indicated, a sleep recording, will help the clinician to make an accurate diagnosis and thus identify the best treatment. Nonpharmacologic methods such as behavioral techniques and cognitive therapies as well as pharmacologic approaches and combinations of these methods should be used for the treatment of sleep problems in hemodialysis patients.

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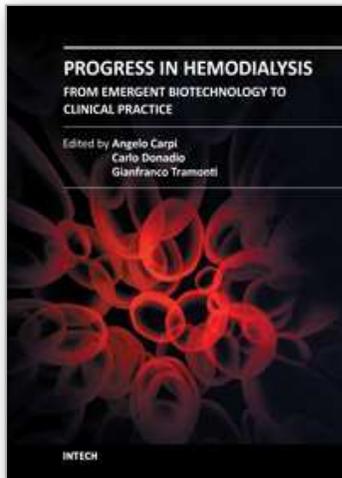
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Edited by Prof. Angelo Carpi

ISBN 978-953-307-377-4

Hard cover, 444 pages

**Publisher** InTech

**Published online** 07, November, 2011

**Published in print edition** November, 2011

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### **How to reference**

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Mukadder Mollaoğlu (2011). Sleep in Patients with ESRD Undergoing Hemodialysis, Progress in Hemodialysis - From Emergent Biotechnology to Clinical Practice, Prof. Angelo Carpi (Ed.), ISBN: 978-953-307-377-4, InTech, Available from: <http://www.intechopen.com/books/progress-in-hemodialysis-from-emergent-biotechnology-to-clinical-practice/sleep-in-patients-with-esrd-undergoing-hemodialysis>

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