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Risk Factors and Treatment of Restless Legs Syndrome in Adults

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1. Introduction

Restless legs syndrome (RLS) is a common clinical entity consisting of an uncomfortable sensation in one's legs and irresistible urge or desire to move them usually occurring in the evening. This syndrome has been sub optimally diagnosed in the past and remains overall misunderstood and under-recognized by many primary health care providers. However, RLS is increasingly recognized to cause significant disease burden and decreased quality of life (Kushida C et al., 2007). The initial modern clinical description was published by Ekbom in 1945 but was largely ignored until the late 1980s when there was a resurgence of interest in RLS (Walters AS & Hening W, 1987). Because of ongoing clinical confusion and the need for more clear epidemiologic assessment, a research group was organized in 1995 and the original IRLSSG criteria were developed (Walters AS, et al., 1995). In 2003, the International Restless Legs Syndrome Study Group (IRLSSG) issued revised guidelines to assist in clinical diagnosis and research of RLS (Allen RP et al., 2003).

2. RLS description and diagnosis

RLS is described by the RLS foundation as a neurological condition that is characterized by the irresistible urge to move the legs. Patients will describe an uncomfortable itching or "creepy-crawling" sensation on the legs in the evenings and report that it feels like "bugs crawling under the skin." The IRLSSG has listed 4 essential criteria to clinically diagnose RLS. Physical examination is usually normal. There is no single test used which will make the diagnosis although many patients suffer from iron deficiency with low ferritin levels. While overnight polysomnography (PSG) in a sleep laboratory is helpful to assess periodic limb movements of sleep (PLMS), a PSG is not necessary to make the clinical diagnosis of RLS. PLMS are defined as a repetitive or periodic bursts of leg (or arm) electromyographic (EMG) activity during sleep associated with discrete, stereotypical movements of the legs or arms. PLMS are felt to be a related but separate disease from RLS. Although most (80%) patients with RLS with have PLMS on PSG testing, approximately 12-20% of RLS patients will not have evidence for PLMS (Montplaisir J et al., 1997). Approximately 30% of patients with PLMS will have RLS symptoms. The revised 2003 IRLSSG essential criteria include 1) An urge to move the legs accompanied or caused by uncomfortable sensations in the legs, 2) The urge to move or unpleasant sensations beginning or worsening during periods or rest or inactivity such as lying or sitting, 3) The urge to move or unpleasant sensations are partially or totally relieved by movements such as walking or stretching, at least as long as

the activity continues, 4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (Allen RP et al., 2003). Despite these revised guidelines, there are still difficulties in excluding mimics such as leg cramps that can confound the diagnosis and the specificity of the 4 diagnostic criteria is 84% (Hening WA et al., 2009). It has been suggested that the validated self-completed Cambridge-Hopkins RLS questionnaire (CH-RLSq) is more useful with a sensitivity of 87.2% and a specificity of 94.4%. (Allen RP et al., 2008). In addition to the diagnostic criteria, the IRLSSG developed a validated, patient-completed 10 item severity rating scale called the IRLS severity scale or IRLSSS (Walters AS et al., 2003).

3. RLS prevalence

RLS has been mainly studied in North America and Europe and appears to have a prevalence of 5 to 15% with up to a 2:1 female ratio (Berger K et al., 2004, Phillips B et al., 2000). Prevalence is markedly higher in certain groups such as Icelandic women where RLS prevalence was found to be 24.4% (Benediktsdottir B et al., 2010). Of interest, the increased risk of RLS in women appears to be linked to parity with an increased risk of RLS directly proportional to the number of children (Berger K et al. 2004). In contrast, nulliparous women have the identical risk of RLS as men the same age. While, most of the epidemiology of RLS has been researched in Europe and North America, there are studies from other areas. Research from Asia appear to yield lower prevalence rates. (Chen NH et al., 2010). Overall, the prevalence of RLS appears to be higher in North American/European populations, especially in women.

4. RLS pathogenesis

The scientific basis of RLS remains unclear but appears to be related in part to the dopaminergic pathways and iron metabolism in the substantia nigra. In 2003, Connor et. al. published an autopsy-based study suggesting that the cause of RLS was related to a defect in the regulation of transferrin receptors in the brain (Connor JR, et al., 2003). In addition, MRI, PET, and SPECT imaging studies have likewise shown alterations in the dopaminergic receptors of the brain (Michaud M et al., 2002). Recently, further evidence has accumulated to support that there is a primary iron insufficiency leading to an overly activated dopaminergic system (Connor JR et al., 2009, Quiroz C et al., 2010). Low iron levels can increase extracellular dopamine and decrease D2 receptors (Earley CJ et al., 2011). Thus, overall the pathophysiologic basis of RLS is not fully understood but there is increasing evidence of iron deficiency related dopaminergic abnormalities. In addition to dopamine and iron physiology, there are clear familial clusterings and genetic linkages. In 2007, researchers in Iceland reported on the first genetic variant associated with a susceptibility to periodic limb movements of sleep (Stefansson H et al., 2007). A total of 4 main genetic variants have since been discovered which account for approximately 80% of primary RLS.

5. Primary RLS

RLS is divided into two main categories which are primary (idiopathic) RLS and secondary RLS. Patients with primary RLS tend to have onset at an earlier age, often under age 45. In addition, there is a significantly higher family history of RLS (Allen RP & Earley CJ, 2000).

6. Clinical associations with RLS or secondary RLS

6.1 RLS and multiple sclerosis

After an initial 2002 meeting presentation where data from 100 multiple sclerosis (MS) patients with a prevalence of RLS of 32%was described, Auger et al reported a prevalence of 37.5% in their 200 French-Canadian MS patients meeting the 2003 IRRLSG criteria. Interestingly, in their patient population, more women than men met RLS criteria and 30% of patients reported that RLS symptoms started or worsened during pregnancy. A positive family history for RLS was reported by 36% of these French-Canadian patients meeting RLS criteria. They speculated whether MS plaque formation and involvement in the basal ganglia may be pathogenic for RLS in these patients. This concept may be supported by the therapeutic effect of dopaminergic therapeutic agents. The concept of potential common susceptibility genes for both MS and RLS is raised by the authors (Auger C et al, 2005). The following year, Kilfoyle et al reported a myelin protein zero (MPZ) mutation which was associated in the individuals studied with various neurological manifestations including RLS and MS (Kifoyle DH, et al, 2006).

In 2007, Manconi et al examined prevalence of RLS in an Italian population of MS patients. In this population of 156 patients, 100 were female and a prevalence of 32.7% was found who met the 2003 IRRLSG diagnostic criteria. However, in contrast to the French-Canadian population, a positive family history for RLS was only reported by 5% of the (total) population. In the majority of these patients (> 90%), RLS symptoms followed or were simultaneous in onset with MS clinical features onset. The authors speculate that the co-existence of MS and RLS may be the result of a particular lesional pattern (Manconi et al, 2007). In a subsequent study of 82 MS patients of whom 30 patients had co-existing RLS, brain and cervical spinal cord MRIs were done. The MS and RLS patients were observed to have a greater degree of cervical cord involvement than those MS patients without RLS. The authors state that cervical cord damage represents a significant risk factor for RLS in MS patients (Manconi et al, 2008).

The Italian REMS Study Group, published the 'REstless legs syndrome in Multiple Sclerosis' or REMS study in 2008 in the journal SLEEP. This group reported a prospective, multicenter case-control epidemiologic survey which involved 20 sleep centers certified by the Italian Association of Sleep Medicine and included 861 MS patients and 649 control patients. They reported a 19% prevalence of RLS, using the IRRLSG criteria, in the MS patients compared to a 4.2% in the control population. This provided a relative risk for RLS in the MS patients of 5.4. Risk factors associated with RLS in the MS patients were identified as older age, longer duration of MS, the primary progressive form of MS, higher global, pyramidal, and sensory disability and the presence of leg jerks before sleep onset. Additionally, RLS symptom severity was reported to be worse in the MS patient group compared to symptoms of control group patients with RLS. The authors comment that their results strengthen the hypothesis that MS inflammatory lesions may induce a secondary form of RLS (The Italian REMS Study Group, 2008).

In a study of French patients with MS by Douay et al, the authors report a prospective evaluation of 242 MS patients and found 18% met the international RLS criteria, consistent with the REMS study report. In this French population, the authors reported RLS symptoms to be more frequent in patients with the relapsing-remitting form of MS (Douay et al. 2009).

A Brazilian study of 44 MS patients reported by Moreira et al, found 27% of their patients met the RLS criteria. The authors did not observe any association of specific patient

characteristics associated with the presence of RLS compared to those MS patients not meeting RLS criteria, in this small prevalence study (Moreira et al, 2008).
Deriu et al published a case-control study of Italian MS patients. The authors enrolled 202 MS patients and 212 age and gender matched healthy controls. Interestingly, 45% of the MS patients met the IRRLSG diagnostic criteria for RLS, however, after neurologic review and examination of the each patient who responded positively to the questionnaire instrument, only 14.6% of the MS patients were felt to truly have a diagnosis of RLS. In the control group, 16.03% were positive responders to the questionnaire criteria, but only 2.8% had a final diagnosis of RLS following neurologic review and examination. The authors comment on the high false positive number of questionnaire responders (Deriu et al, 2009).
In summary, there is evidence of an increased prevalence of RLS in the MS population. Several interesting possibilities have been suggested to explain this association. The weight of evidence seems to support the concept of a secondary RLS likely arising from strategic geographic involvement of demyelinating lesions.

6.2 RLS and other neurologic disorders

Peripheral neuropathy has also been associated with RLS. A recent case-control study (Hattan E et al 2009) in a Quebec population examined 245 patients with a diagnosis of peripheral neuropathy and 245 age and gender matched controls. The authors considered a positive response to three of the four essential criteria to be 'screen-positive'. All 'screen-positive' patients were subsequently evaluated by a blinded movement disorders specialist. Of the 245 peripheral neuropathy patients, 26.5% were 'screen-positive', compared to 10.2% of controls. Confirmation by neurologist, however, revealed only 46% of the 'screen-positive' peripheral neuropathy patients were felt to truly have a diagnosis of RLS compared to 80% of the 'screen-positive' control patients. After this diagnostic confirmation, the overall prevalence of RLS did not differ between the peripheral neuropathy patients and the control group.
The prevalence of RLS was evaluated in a cohort of 99 Italian patients with acquired diabetic peripheral neuropathy (Gemignani et al, 2007). Using IRRLSG diagnostic criteria, RLS was found to be present in a third of the patients in this study population (33/99). The authors reported that of the various forms of diabetic neuropathy represented within this population, small fiber sensory neuropathy was more common than other forms. A prominent symptom associated with RLS was 'burning feet'. The authors suggest that RLS may be triggered peripherally by abnormal sensory inputs from small fibers.
A case series of 12 patients with essential mixed cryoglobulinemia and associated peripheral neuropathy reported a frequency of RLS, using pre-2003 diagnostic measures, of one third (4/12) (Gemignani et al, 1997).
A recent report (Bachmann CG et al 2010) suggest response to specific stimuli may be able to distinguish between primary RLS and RLS secondary to small fiber neuropathy. In this study of 21 primary RLS patients and 13 patients with secondary RLS related to small fiber neuropathy, the authors describe thermal hypoesthesia to cold and warm in those with secondary RLS compared to both the primary RLS study patients and controls. They also suggest support for the RLS pathogenesis concept of central disinhibition of nociceptive pathways which might be induced by conditioning afferent input from damaged small fiber neurons in secondary RLS.
Restless legs syndrome has been reported as increased in prevalence in German hereditary spastic paresis patients (Sperfeld AD, et al, 2007) and in Argentinian patients with Fabry's disease (Dominguez RO, et al, 2007). RLS has also been reported to be present in 18.1% of

227 Charcot-Marie Tooth disease patients compared to 234 controls with a 5.6% prevalence. RLS severity was correlated with worse sleep quality and reduced health-related quality of life measures. Variation in prevalence was not observed between subtypes of Charcot-Marie Tooth disease, but women were more severely affected by RLS than male patients (Boentert M, et al 2010). A series of 28 patients with Friedreich's Ataxia were surveyed for prevalence of RLS with 32% meeting diagnostic criteria (Synofzik M et al, 2011). In a population of 28 chronic inflammatory demyelinating polyneuropathy (CIDP), a prevalence of 39.3% for RLS was found, compared to 7.1% prevalence in age and gender matched control patients.

Isolated case reports of RLS symptomatology following development of hyperparathyroidism (Agarwal P et al, 2008), administration of interferon therapy (LaRochelle JS, et al, 2004), development of multifocal motor neuropathy (Lo Coco D, et al, 2009), and Guillain-Barré syndrome have been reported (Marin LF, et al, 2010). Additionally, a case report has been published reporting a patient who experienced remission of severe RLS following excision of multiple foot neuromata (Lettau LA, et al 2010).

The question has also been raised as to whether RLS in seen in a higher prevalence in patients with Parkinson's Disease. This has been addressed in an Italian population of 118 Parkinson's Disease outpatients using a case-control study design. The authors report a failure to demonstrate increased prevalence of RLS in the Parkinson's patients in comparison to age and gender matched control patients. They further acknowledge the RLS prevalence assessment may be impeded by the concurrent treatment of Parkinson's Disease with dopaminomimetic drugs, which may also be expected to impact on RLS symptomatology (Calzetti et al, 2009). Another study from the Netherlands in 269 non-demented Parkinson's Disease patients, found RLS to be present in 11% of patients. RLS severity was noted to correlate positively with Parkinson's Disease severity. RLS was also significantly more common in male patients than female. The authors note the similar prevalence of RLS in their study population to the general population and submit that this could potentially relate to concurrent dopaminergic therapy. They also suggest that in view of the relationship of severity of RLS to severity of Parkinson's Disease related primarily non-dopaminergic symptoms, that non-dopaminergic systems may play a role in any potential relationship between RLS and Parkinson's Disease (Verbaan D, et al, 2010).

In a reverse style of assessment, 23,119 participants in the Health Professional Follow-up study who were free of diabetes and arthritis were surveyed. The IRRLSG diagnostic criteria were applied and concurrent diagnoses of Parkinson's Disease were investigated. The adjusted odds ratios for Parkinson's Disease in men with RLS symptoms with frequency from 5-14 times per month was 1.1, and in those with a frequency of RLS of 15 or more times per month the odds ratio was higher at 3.09. The authors concluded that men with RLS symptomatology were more likely to have concurrent Parkinson's Disease (Gao X, et al, 2010).

6.3 RLS and pregnancy

Lower extremity symptoms consistent with RLS have been reported in pregnancy. In a study of 642 pregnant Italian women, data was collected around the time of delivery and at follow-up evaluation up to six month post-delivery. Patients were screened with the IRRLSG diagnostic criteria. The authors reported that 26% of women acknowledged symptoms of RLS during their pregnancy. It was most strongly related to the last trimester of the pregnancy and tended to disappear around the time of delivery. The authors concluded that pregnancy was associated with transient RLS. They did also observe that women with RLS symptoms had lower hemoglobin levels and MCV compared to healthy

subjects. (Manconi M et al, 2004). An American study of 189 nulliparous women who were enrolled between six and 20 weeks of gestation and were followed up in the third trimester, reported an increase in patients meeting RLS criteria from 17.5% at enrollment up to 31.2% in the third trimester (Facco FL, et al, 2010).

In a questionnaire study of female members of the French Association of Patients with RLS, Ghorayeb et al applied both the International RLS Severity Scale (IRLSSS) and a questionnaire addressing reproductive behaviour and RLS history. Interestingly, women who had had a pregnancy showed a higher mean IRLSSS score than women who had never had a child. Worsening of symptoms during pregnancy were reported by 23% of patients, 29% of non-menopausal women reported increased severity of RLS symptoms during menses, and 69% of women reported worsening of symptoms following menopause (Ghorayeb I, et al, 2008). An Australian case-control study of pregnant women demonstrated a RLS prevalence of 22.5% of 211 women. A positive family history of RLS and of 'growing pains', as well as a personal childhood history of 'growing pains' were associated with meeting RLS criteria in this study population (Balendran et al 2011).

In a Turkish study of 146 pregnant women, 38 were diagnosed with RLS. The authors report lower hemoglobin levels to be a risk factor for RLS in pregnancy (Tunc et al 2007). In a study of pregnant women in Pakistan, 81 of 271 women met diagnostic criteria for RLS. The authors reported anemia and a positive family history of RLS to be predictive for development of de novo RLS, whereas, a positive family history for RLS and multiparity were predictors for pre-existing RLS with odds ratios of 12.39 and 6.84 respectively (Sikandar R, et al, 2009). A previous pregnancy was also identified by Pantaleo NP et al as a significant risk factor for RLS in a re-analysis of data from a prior RLS study. They observed that in family members of RLS probands, the prevalence of RLS was significantly higher for parous women (49.5%) than for nulliparous women (33.7%) or for men (30%). These differences were not observed in control proband family members. The authors suggest that in patients with a positive family history of RLS, pregnancy has a major influence on the risk of developing RLS (Pantaleo NP, et al, 2010).

Examining hormonal influences on RLS, Dzaja et al, studied 10 pregnant German women with RLS and nine healthy pregnant controls. Blood hormone levels of estradiol were higher in patients with RLS than in control patients. The authors suggest estrogens may contribute via a pathophysiological mechanism to triggering of RLS symptoms during pregnancy (Dzaja A, et al, 2009).

Neau et al, in a cross-sectional questionnaire study of 1.022 pregnant French women from a single town, screened for RLS using IRRLSG criteria. They found 24% of these women to be affected by RLS during their pregnancy. The symptoms of RLS were strongly related to the third trimester of the pregnancy. In a follow-up study of a smaller number of patients, the authors report resolution of RLS symptoms within a short time interval following delivery in the majority of women (Neau JP et al, 2010a, Neau JP et al, 2010b). A follow-up study of RLS in pregnant Italian women performed after a mean lapse of 6.5 years, reported on 74 women with pregnancy associated RLS and 133 women who did not have RLS symptoms during their pregnancy. During the time between the original study and this follow-up investigation, the prevalence of RLS had increased to 56% person/year in women who had experienced RLS symptoms transiently during their pregnancy and 12.6% person/year in subjects who had not been troubled with RLS symptoms during pregnancy. The authors conclude the transient pregnancy RLS form to be a significant risk factor for development of a future chronic form of RLS (Cesnick et al, 2010).

6.4 RLS and renal disease

Renal disease has been associated with RLS symptomatology. A recent hospital based study of 301 patients, revealed a prevalence for meeting RLS criteria of 18.3%. Multivariate analysis identified iron deficiency and chronic renal disease to be independent predictors for RLS in this population (Quinn C et al, 2011). In a Japanese study of 490 uremic patients on hemodialysis (HD), 12.2% were found to meet criteria for RLS. The authors found a relationship between RLS, anxiety, anemia and high serum phosphorus level. They failed to find evidence of previously identified risk factors including relationship to gender, longer duration of HD therapy, frequency of HD sessions, and smoking (Takaki J et al, 2003). The significance of an elevated serum phosphorus in RLS is unclear.

A lower frequency of RLS was observed in an Indian study of 121 HD patients and 99 controls, where only 6.6% of HD patients and 0% of controls met RLS criteria. Nerve conduction studies conducted on RLS patients found the majority to have evidence of sensori-motor neuropathy (Bhowmik D, et al, 2003). Another prevalence study in Brazil in 176 HD patients observed a prevalence of RLS of 14.8% (Goffredo et al, 2003). A similar prevalence was established in 894 dialysis patients participating in the CHOICES (Choices for Healthy Outcomes In Caring for End Stage renal disease) study, where a prevalence of 15% for 'severe' RLS was observed. Age and diabetes were positive predictors for RLS in this population. The authors also report an increase in the adjusted mortality hazard ratio of 1.39 in patients with severe RLS. Reduced quality of life measures in these patients was also observed (Unruh ML, et al, 2004). In a small study from the Netherlands, 48 patients with renal disease and RLS were studied by polysomnogram (PSG) and questionnaire. A prevalence of 58.3% for meeting RLS criteria was observed. In addition the authors report nearly all RLS patients had evidence of severe periodic limb movement disorder on PSG (Riisman RM, et al, 2004). Examining a population who were not yet dialysis dependent, Merlino et al enrolled 138 chronic renal failure patients and 151 controls. RLS criteria were met by 10.9% of the chronic renal failure group and 3.3% of the control population. An association with iron deficiency and female gender was observed (Merlino et al, 2005).

6.5 RLS and rheumatic diseases

In the rheumatoid arthritis (RA) patient population, increased prevalence of RLS has been reported by several investigators. Reynolds et al studied hospitalized RA patients employing a 'control' group of osteoarthritis (OA) patients, and found a 30% prevalence of RLS in RA compared to 3% in OA (Reynolds G et al, 1986). A subsequent study again comparing RA and OA found comparable prevalence rates for RLS of 25% in RA and 4% in OA (Salih AM, et al, 2004). Auger et al in their study of MS patients employed a RA patient group for contrast, finding a prevalence rate for RLS of 31% in their RA group (Auger C, et al, 2005). A more recent study employing the 2003 IRRLSG criteria for RLS found a prevalence of RLS of 27.7% in RA and a prevalence of 24.4% in OA patients (Taylor-Gjevre, et al, 2009). Increased frequency of RLS has also been reported in other rheumatic disease populations, including Sjogren's Syndrome, scleroderma and fibromyalgia patients (Taylor-Gjevre, et al, 2011). A recent study of RLS in Systemic Lupus Erythematosus patients has also suggested an increased prevalence in that population (Hassan N, et al, 2011).

6.6 RLS and Iron deficiency

An increased prevalence of anemia or iron deficiency has been observed in many RLS patient populations. Treatment with iron supplementation has been efficacious in many cases of RLS

in patients with low serum ferritin levels. This is discussed in greater depth in the treatment section of this chapter. Consistent with these observations, there has been an increased prevalence of RLS in patients with celiac disease, a disorder with associated abnormal iron absorption (Moccia M, et al, 2010) and as mentioned previously in this chapter, many instances of secondary RLS appear to be also associated with anemia or low iron status.

There have been several studies assessing prevalence of RLS in regular blood donors. A large Swedish study of 946 consecutive blood donors, aged 18-64, who were evaluated for RLS, found a gender difference in prevalence. In male blood donors 14.7% met RLS criteria, in female donors the frequency increased to 24.7%. Further, in patients with laboratory evidence consistent with iron-deficiency, the frequency of RLS increased to 37.5%. The authors conclude RLS to be common amongst female blood donors (Ulfberg J, et al, 2004). Conversely, in an American study of 144 blood donors, only a 4% prevalence of definite RLS was appreciated. The authors comment that their relatively small sample size may influence their results (Arunthari V, et al, 2010).

From a pathologic viewpoint, decreased iron content has been observed in the substantia nigra which is felt to contribute to the pathophysiology of RLS (Synder AM, et al, 2009). In a recent study, Connor et al examined expression of iron management proteins in proximity to the blood-brain interface in brains from eleven RLS patients and in 14 control brains. The authors report a significant decrease in heavy chain ferritin, transferrin and it's receptor in the microvessels in RLS patients compared to controls. Additionally, activity of an iron regulatory protein was observed to be diminished in the RLS patients compared to controls. These relative differences between brains from RLS patients and control patients suggest fundamental differences in brain iron acquisition in RLS patients (Connor JR, et al, 2011)

7. Treatment options for RLS

Historically, there were a variety of treatments for RLS ranging from bloodletting to opiates. Indeed, Sir Thomas Willis over 325 years ago described the first probable case of RLS and used opium to alleviate the symptoms. When RLS was "rediscovered" by researchers in the 1980s, once again opioid narcotics were the treatment of choice (Hening WA, et al. 1986). In that study, five patients with RLS were given opioid drugs which relieved their awake RLS symptoms as well as PLMs and sleep disturbance. When counteracted with intravenous naloxone, the RLS symptoms and findings returned leading the authors to speculate on the endogenous opiate system playing a role in RLS pathogenesis. However, with increasing research in the last two decades, it has become clear that the underlying pathology of RLS is largely due to alternations in dopaminergic pathways. This has lead to the use of both non-specific and specific dopamine receptor agents.

7.1 Pharmacological treatments for RLS

7.1.1 Iron replacement therapy

While Ekbom did recognize the possible role of iron therapy in RLS, it was not until 1994 when O'Keeffe in Dublin did the first clinical trial of iron replacement therapy. In that study of 18 elderly patients with 18 matched controls, iron status and RLS response to iron therapy was observed. The researchers found that serum ferritin levels were reduced in RLS subjects compared to the control group and that levels were inversely correlated to the severity of RLS symptomatology. In the 15 RLS patients treated with iron replacement therapy for 2 months, there was a significant improvement in RLS symptoms (O'Keeffe ST, 1994). In a

recent double-blinded, placebo-controlled study, Wang and colleagues showed the benefit of iron replacement in RLS patients with low serum ferritin. In this study, 373 patients were screened and 157 (42%) met the 2003 IRLSSG criteria for RLS. Of these, there were only 18 patients who consented to participate and met the inclusion criteria (which included having a low-normal serum ferritin between 15-75 ng/ml). Eleven patients were randomized to iron replacement (ferrous sulfate 325mg po bid) and 7 to placebo for 12 weeks and IRLS scores were obtained at the start and end of the study. The researchers found a clinically significant ($p = 0.01$) improvement in IRLS scores in the iron therapy group and a non-significant ($p = 0.07$) trend towards improvement in quality of life (Wang J, 2009).

7.1.2 Dopamine precursors

Dopamine is a catecholamine which acts as a neurotransmitter but cannot cross the blood-brain barrier. Levodopa (L-DOPA) is a precursor to dopamine (as well as norepinephrine and epinephrine) and can cross the blood-brain barrier. Once in the brain, L-DOPA is converted by DOPA decarboxylase to dopamine which can act on the dopamine receptors to treat RLS. However, because peripheral L-DOPA is also converted to dopamine leading to adverse effects, L-DOPA is usually given with a peripheral DOPA decarboxylase inhibitor (usually carbidopa). There is a large body of evidence supporting the effectiveness of L-DOPA in RLS. One of earliest randomized trials was done in the USA and published in 1993. This study was a randomized, double-blind, placebo-controlled, cross-over design trial evaluating carbidopa/levodopa with proproxyphene and placebo. The primary outcome was PSG measurements and sleep latency tests. The researchers found that carbidopa/levodopa normalized the PLMs and improved sleep, especially in the first 3 hours of sleep (Kaplan PW et al., 1993). However, it soon became apparent that carbidopa/levodopa had a serious drawback in regards to augmentation or rebound of RLS symptoms the following morning and/or early afternoon. In a report from 1996, Allen and colleagues prospectively evaluated 46 consecutive patients being treated with carbidopa/levodopa. They found that 82% of RLS patients and 31% of PLMS patients experienced augmentation problems and this was severe enough to lead to medication changes in 50% of the RLS patients (Allen RP, Earley CJ, 1996). Because of augmentation issues, other researchers have evaluated using sustained-release L-DOPA preparations. Trenkwalder and colleagues did an open-label extension trial of an earlier double-blinded, cross-over study evaluating standard and sustained-release L-DOPA. In this 1 year trial they found that 60% of patients discontinued therapy due to aggravating daytime symptoms (Trenkwalder C et al., 2003). In a 2006 review, Paulus & Trenkwalder examined the world literature and concluded that augmentation is a result of severely increased dopamine concentration in the CNS and that overstimulation of the D1 receptors compared to the D2 receptors in the spinal cord may cause discomfort and PLMS. Also, iron deficiency may be a significant predisposing factor for the development of augmentation. The researchers concluded that therapy with L-DOPA or dopamine agonist should endeavour to be low-dose and that iron replacement and/or opiates are the therapies of choice to use with augmentation (Paulus W & Trenkwalder C, 2006). In summary, L-DOPA is a widely available and inexpensive therapy for RLS which has been shown in numerous studies to be beneficial in improving objective PSG findings as well as subjective measures of sleep and RLS symptoms. Unfortunately, there are problems particularly linked to L-DOPA with next morning augmentation of RLS symptoms. This does impair the usefulness of L-DOPA especially when there are newer effective dopamine agonists with a better side effect profile.

7.1.3 Ergot-derived dopamine agonists

Ergotamine is related to ergot alkaloids and is structurally similar to several neurotransmitters including dopamine. Ergotamine derivatives include bromocriptine, pergolide, and cabergoline. It most be noted that all ergot derivatives have been associated with cardiac valve disease. In a recent Italian study, researchers found that patients taking pergolide or cabergoline had a relative risk of 4.2 to 6.3 for valve regurgitation compared to patients using non-ergot dopamine agonists and controls (Zanettini R, 2007). Thus it is recommended to conduct close cardiac monitoring in patients on ergot-derived dopamine agonists.

Bromocriptine is an ergot-derivative dopamine agonist that preferentially acts on the D2 dopamine receptor. It has traditionally been used in the treatment of pituitary tumors and Parkinson Disease but has been tried for RLS with some efficacy. In a small, double-blinded, randomized crossover study, researchers found that 83% of patients had partial subjective improvement in RLS symptoms but no significant change in PLMD by PSG (Walters AS, 1988). A more recent study from Europe compared bromocriptine to pramipexole (a preferential D3 receptor agonist) showing that while both helped to improve RLS symptoms, pramipexole was superior. In addition, pramipexole improved PSG parameters including PLM frequency (Manconi M, 2011). Thus, bromocriptine is not commonly used as a therapy for RLS at this time.

Pergolide is a semi-synthetic ergot-derivative that acts as a dopamine agonist at both the D2 and D1 receptors. In a major study, Trenkwalder and colleagues found pergolide significantly improved RLS symptom severity and PLMD (Trenkwalder et al. 2004). The researchers conducted a double-blinded, placebo-controlled, randomized study of pergolide therapy; the Pergolide European Australian RLS (PEARLS) study. In this study, 100 patients with primary (idiopathic) RLS were randomized to either pergolide or placebo for 6 weeks. In addition, there was a 12 month follow-up phase with open-label pergolide for placebo non-responders. PLMS were assessed by PSG and RLS symptoms by the IRLS severity scale (IRLSSS) questionnaire. They found that pergolide significantly improved IRLSSS results at 6 weeks. In addition, the pergolide treated patients had substantial improvements in the 6 week and 12 month PLM index. The authors concluded that pergolide significantly improves PLM findings as well as subjective RLS sleep disturbance.

Cabergoline is a newer, semi-synthetic, long-acting, ergot-derivative dopamine agonist that particularly acts on the D2 receptors but also has some affinity for the D1 and D3 receptors. One of the earliest studies examining cabergoline in RLS was from Germany in 2000. In that study, researchers conducted a 12 week open label trial assessing efficacy with baseline and 12 week PSG and RLS subjective questionnaires. The research team found improvements in PLMs and subjective relief of symptoms and concluded that cabergoline was effective and well-tolerated (Stiasny K et al., 2000). A more recent randomized, double-blinded, placebo-controlled, multicenter PSG study examined the efficacy of cabergoline in RLS (the CATOR study). In this study, 40 patients with moderate to severe RLS were randomized to either cabergoline or placebo for 5 weeks. Baseline and end of study PSGs were obtained as well as IRLSSS and quality of life questionnaires. The researchers found the cabergoline group had significant improvements in PSG parameters, IRLSSS severity scores, and the RLS quality of life scores. They concluded that cabergoline is an efficacious and well-tolerated therapy for RLS symptoms and associated sleep abnormalities (Oertel WH et al., 2006). Unfortunately, like pergolide, cabergoline has been implicated in cardiac valvular heart disease and patients treated with this agent need close cardiac monitoring.

7.1.4 Nonergot-derived dopamine agonists

There are three newer fully-synthetic dopamine agonists that are not derived from ergot. The three drugs include ropinirole, pramipexole, and rotigotine. As of July 2011, rotigotine is not approved by the FDA for use for RLS in the USA. These nonergot agents are not associated with valvular heart disease but have been associated with impulse control disorders including pathological gambling, compulsive overeating, hypersexuality, and pyschosis. There is increasing recognition that patients treated with these agents should be monitored for impulse control disorders.

Ropinirole acts as a dopamine agonist primarily on the D3 as well as D2 & D4 receptors. It was originally studied in the early 1990s for Parkinson's Disease and later found to be beneficial for RLS. Ondo studied 16 RLS patients in an open-label trial of ropinirole. Three patients discontinued ropinirole use. Of the remaining 13 patients, the average duration of use was 3.9 months and there was a 58.7% improvement in symptoms (Ondo W, 1999). Further studies reinforced the safety and efficacy of ropinirole in RLS. The TREAT RLS 1 study (Therapy with ropinirole; efficacy and tolerability in RLS 1) was a randomized, double-blinded, placebo-controlled trial of 12 weeks duration. 146 subjects were randomized to the ropinirole group and 138 to the placebo group. The key endpoint was the IRLS severity score which showed significant improvement in the ropinirole group over the placebo group at week 12 ($p=0.0036$). The researchers concluded that ropinirole improves RLS compared with placebo and was generally well-tolerated (Trenkwalder C et al. 2004). More recent similar studies from the USA and Canada confirm the efficacy and safety of ropinirole, including long-term duration in the Canadian study. In the USA study, Bogan and colleagues studied 331 subjects in a multicenter, double-blinded, placebo-controlled, flexible dose trial of 12 weeks duration. The primary endpoint was the IRLS score at week 12 which showed a significant improvement in the ropinirole group ($p<0.001$). In addition, the treatment group showed improvements in subjective measures of sleep disturbance and quantity and quality of life scores also improve. The authors concluded that ropinirole improves RLS symptoms and was generally well-tolerated over a 12 week study period (Bogan RK et al. 2006). In the Canadian study, researchers studied the long-term efficacy (36 weeks) of ropinirole and also evaluated for the potential of symptom relapse after drug discontinuation. They identified 202 patients and found significantly fewer subjects relapsed in the ropinirole arm compared to placebo (32.6% versus 57.8%, $p=0.0156$). In addition, the time to relapse symptoms was longer in the ropinirole group and less patients withdrew from lack of efficacy in that group. The authors concluded that ropinirole was highly efficacious and well-tolerated over a 36 week period (Montplaisir J et al. 2006). In 2008, Allen and colleagues reviewed RLS age-of-onset and the response to treatment. They observed no relationship between the RLS symptoms age-of-onset and baseline IRLS score, and between dose administered at week 12 and age-of-onset. The authors concluded that ropinirole provides effective RLS symptom relief that is not affected by age of symptom onset (Allen RP, Ritchie SY, 2008). In 2009, a large meta-analysis was conducted to evaluate the effect of ropinirole versus placebo on sleep outcomes as measured by the Medical Outcomes Study (MOS) sleep scale. The validated MOS sleep scale is a 12 question scale which evaluates sleep disturbance, sleep adequacy, snoring, somnolence, quantity of sleep, and other measures. In this review, the authors found that ropinirole improved sleep quality and decreased daytime somnolence in patients with primary RLS (Hansen RA, et al., 2009). Finally, researchers assessed the efficacy of ropinirole on depressive symptoms and RLS. In a multicenter, randomized, double-blinded, placebo-controlled trial, 231 patients with

moderate to severe primary RLS and at least mild depression were studied. Ropinirole versus placebo was given for 12 weeks with measurements obtained at baseline and 12 weeks for the Montgomery-Asberg Depression Rating Scale, the Hamilton Scale for Depression and Beck Depression Inventory-II score, and the Medical Outcomes Study sleep scale. There were significant improvements in the Montgomery and Hamilton scores as well as 3 of the 4 domains of the MOS sleep scale. The authors concluded that in patients with RLS and mild to moderate depression, appropriate therapy for RLS should first be tried and antidepressant medication may be needed later if the depression symptoms still persist (Benes H et al., 2011). In summary, ropinirole is a newer nonergot-derived dopamine agonist with a particular affinity for the D3 dopamine receptors. It has been shown to be beneficial in RLS symptom improvement both short and long-term with improvement in daytime somnolence and quality of life indicators.

Pramipexole is a nonergot-derived dopamine agonist that acts on the D3 as well as D2 and D4 receptors. One of the earliest RLS studies was conducted by Lin at the Mayo Clinic in 1998. In that research, 16 patients were studied who had failed other dopaminergic therapies for symptomatic RLS. An open-label trial showed that after 2 to 3 months usage, there was clinically significant improvements in nocturnal leg restlessness and involuntary leg movements. The authors proposed that pramipexole was an effective therapy for the treatment of RLS (Lin SC et al., 1998). Following that encouraging initial report, a small randomized trial was conducted in Quebec. Researchers studied 10 RLS subjects with PSG and RLS symptom questionnaire using a double-blinded crossover study. They found a significant reduction in PLMs and RLS symptoms of bedtime/nocturnal leg discomfort (Montplaisir J et al., 1999). A larger randomized trial from Finland evaluated the efficacy and safety of pramipexole in 2006. In this study (the PRELUDE study), 109 patients with moderate to severe RLS (based on the IRSS severity score) were randomized in a 3 week, double-blinded, placebo-controlled, dose-finding study. PSG measures and IRLS severity scores were assessed. At all doses, the PLM index was reduced and IRLS severity scores reduced. The authors concluded that pramipexole was an effective and safe therapy for treatment of both the objective (PSG measures) and subjective (IRLS severity) aspects of RLS (Partinen M et al., 2006) In a long-term 52 week open-label study, Japanese researchers found that pramipexole was both effective and safe (with no RLS augmentation), especially in patients with an IRLS score less than 20 (Inoue Y, et al., 2010). In a more recent, multicenter trial, pramipexole was evaluated for efficacy and augmentation problems over a 6 month period. This was a 6 month, randomized, double-blinded, placebo-controlled trial in which 321 patients were recruited. Primary endpoint for efficacy was the change in the IRLS severity score. In addition, patients maintained a symptom diary and cases that met pre-defined criteria for suspected augmentation were reviewed by a blinded panel. The study showed that pramipexole was significantly more effective than placebo in improvements of IRLS severity ($p=0.0077$). Over 6 months, the incidence of confirmed augmentation was 9.2% in the pramipexole group versus 6.0% in placebo and the rate increased with treatment in the intervention group but not placebo. Overall, the authors felt that pramipexole was effective and safe but did suggest it should be studied over a longer duration for further assess augmentation issues (Hogl B, et al., 2011). More recent trials evaluating pramipexole has focused on comparison with other dopaminergic agonist. In a recent study by Manconi, pramipexole (mainly a D3 receptor agonist) was compared with bromocriptine (largely a D2 receptor agent) and researchers found that pramipexole was more effective than bromocriptine in reduction of PLMs and that while both drugs reduced RLS symptoms, the

pramipexole group had greater symptom improvements (Manconi M et al., Neurology 2011). The same Italian group also did a recent comparison of pramipexole to ropinirole. Researchers found that both treatment groups improved RLS symptoms and reduced PLMs on PSG compared to the placebo group and that there was no significant differences between the pramipexole and ropinirole treatment arms (Manconi M et al. Mov Disorders 2011). In summary, pramipexole is a newer nonergot-derived dopamine agonist with preferential action on the D3 dopamine receptor site. It has been shown to be beneficial for both objective PSG PLM findings as well as subjective improvements in RLS clinical symptoms. It is generally well-tolerated although there may be an issue with augmentation long-term.

Rotigotine is another newer nonergot-derived dopamine agonist. It is formulated as a once daily transdermal patch and approved to treat RLS in Europe but not FDA-approved for the USA. It appears to mainly work on the D2, D3, and D4 receptor sites. In one of the earliest pilot studies to show benefit for RLS patients, German researchers in 2004 evaluated 63 patients. In this randomized, multicentre, double-blind, parallel-group trial, 63 subjects were studied using the IRLS severity score as the primary endpoint. Researchers found a significant improvement in the treatment group and concluded that transdermal rotigotine was efficacious and well-tolerated (Stiasny-Kolster K et al., 2004). More recently in a multicenter, randomized, double-blind, placebo-controlled 6 month trial, 505 patients with moderate to severe RLS were placed on placebo or rotigotine with the primary endpoints being the IRLS severity score and the CGI-1 score. The treatment group had significantly improved IRLS and CFI-1 outcomes. There was an overall 27% incidence of skin reactions to the transdermal patch. Overall, the authors concluded that rotigotine significantly reduced the severity of RLS symptoms and that treatment effectiveness was maintained throughout the 6 month study period (Hening WA et al., 2010). Rotigotine was also recently assessed in an overnight PSG study evaluating objective PLM measurements. This study was a multicenter, randomized, double-blind, placebo-controlled trial that evaluated 67 subjects over a 4 week period. Baseline and 4 week PSG and subjective questionnaires (IRLS, CGI-1, MOS-S) were obtained. The authors found significant improvements in both the subjective questionnaires but also the objective PSG PLM data. The researchers concluded that rotigotine was effective and well tolerated in the 4 week treatment of both motor symptoms and subjective sleep disturbances caused by RLS (Oertel WH et al., 2010). Finally, in a long term follow-up study, rotigotine was shown to provide sustained effectiveness in treating moderate to severe RLS symptoms for up to 5 years and was generally well-tolerated (Oertel W et al., 2011).

7.1.5 Other pharmacological treatments for RLS

A number of other therapies have be evaluated for RLS including opioids, gabapentin and pregabalin, clonazepam, and case reports of melatonin, buproprion, and other agents. Overall, there is a long experience with opioids and those drugs have been especially useful in dopaminergic resistant RLS with augmentation problems. Clonazepam has also been widely used but is not particularly efficacious and now has been largely replaced by dopaminergic agents. In April 2011, the FDA approved extended release gabapentin for use in moderate to severe RLS. This anticonvulsant agent has recently been shown to be beneficial in RLS and may be especially useful when dopamine agents provide incomplete resolution of RLS symptoms and/or augmentation issues arise. Please remember that the extended release form of gabapentin gives different concentrations of drug than the shorter acting form. Finally, it is important to note that all epilepsy drugs carry a suicide warning label including gabapentin.

7.2 Non-pharmacological treatments for RLS

7.2.1 Exercise

Traditionally, one of the basic clinical recommendations in treating RLS symptoms involves exercise and stretching maneuvers. This has been endorsed by the RLS Foundation (www.rls.org) in their latest patient brochure although the data supporting this is limited. There have been earlier studies by suggesting that exercise close to bedtime is counterproductive for RLS. In a large study, Ohayon assessed the prevalence of RLS and PLMD in the general population. During the multivariate analysis of the secondary results, the researchers (Ohayon, 2002) found that physical exercise close to bedtime (within 2 hours for at least 15 minutes exercise 3 or more times per week) was associated with an increased risk of RLS (OR 1.34, $p<0.05$) and PLMD (OR 1.43, $p<0.05$). However, in a conflicting study from 2000, Phillips et al. found that a lack of exercise was significantly associated with RLS. In a telephone survey of over 1800 participants, a single question (modified from the 1995 IRLSSG criteria) was used to screen for RLS. In this study, there was an age-adjusted prevalence of RLS of 10.0% and a lack of exercise (less than 3 hours/month) was significantly associated with RLS (OR 3.32). In 1996, a Brazilian study evaluated 11 volunteers with to study the effect of acute physical activity on RLS and PLMD. In this report using a baseline PSG followed the next day by exercise and then a repeat PSG, there was a reduction in PLMD noted on the second night PSG (de Mello, 1996). In the only randomized-controlled trial of exercise in RLS, Aukerman studied 28 individuals in a 12 week exercise trial. The average age was 53.7 years and 39% of study subjects were male. Subjects were randomized to either a control group with usual activities or to an exercise group. The exercise program consisted of 3 days a week aerobic and lower extremity resistance/conditioning training. The IRLSSG severity scale and an RLS ordinal severity scale were checked at 0, 3, 6, 9, and 12 weeks. Of the 28 subjects, most (23) completed the trial with 11 in the exercise training group. The researchers found that the exercise group had a significant improvement in RLS symptoms compared to the control group with a $p = 0.001$ for the IRLSSG severity score and $p < 0.001$ for the RLS ordinal scale. The research team concluded that a prescribed exercise program is effective in improving RLS symptoms (Aukerman MM 2006).

7.2.2 Sequential compression devices

There is a hypothesis that reduced blood flow to the extremities may play a role in RLS symptoms. Research has been undertaken to ascertain whether sequential (pneumatic) compression devices may alleviate RLS symptomatology. In a small preliminary study from 2005, researchers from New Jersey evaluated 6 patients using enhanced external counter pulsation (EECP) devices on the legs for one hour daily Monday to Friday for 7 weeks (Rajaram SS, 2004). All 6 patients met the 2003 IRLSSG criteria and were assessed with the IRLS rating scale (IRLSSS) before and after the intervention. It should be noted that 3 subjects did not complete the IRLSSS until 4-5 months after EECP treatment. Further complicating the results, 4 of the 6 patients suffered from diabetic peripheral neuropathy and no electromyography or nerve conduction studies were done before or after EECP treatment to assess any potential neuropathy changes. Nevertheless, the research team found that the IRLS rating scale was significantly improved after EECP intervention and suggested that decreases in vascular flow may affect the nervous system (peripheral or central) causing the sensory symptoms of RLS. In a more rigorous prospective, randomized, double-blinded sham-controlled trial, Lettieri and Eliasson studied 35 subjects in 2009. Consecutive patients attending a sleep clinic for RLS for approached for recruitment. 41 RLS

patients were assessed for eligibility with 6 excluded (4 not meeting inclusion criteria and 2 refused to participate). The remaining 35 patients were randomized into either therapeutic or sham treatment with a sequential compression device for 1 hour daily for 4 weeks. Validated questionnaires were administrated at the start and end of the intervention. These forms included the International Restless Legs Syndrome Study Group Severity Scale (IRLSSS), the Johns Hopkins Restless Legs Severity Scale (JHRLSS), and the restless legs syndrome quality of life instrument (RLS-QLI). Iron therapy and RLS pharmacological use was similar between the sham control and intervention groups. The researchers found significant improvements in the IRLSSS, JHRLSS, and the RLS-QLI for the intervention group and suggest that pneumatic compression devices are a useful adjunctive or alternative therapy for RLS (Lettieri CJ, 2009).

7.2.3 Massage therapy

Massage therapy has been long recommended as an additional therapy for RLS symptoms. However, there is a dearth of scientific evidence to support this claim. In a case report from 2006, Russell presented a 35 year old women with RLS type symptoms. There was no indication whether the patient actually met the 2003 IRLSSG criteria. It was noted that the patient had previously tried ropinirole without benefit. In this case report, the patient was treated with twice weekly massage therapy of 45 minute duration to the lower extremities for a 3 week period and reported improvements on a subjective symptom intensity scale from 40% at baseline to 10% at the end of therapy (Russell M, 2006). Interestingly, 2 weeks following the end of the massage intervention, the patient reported a return of her symptoms. Overall, there is a lack of scientific evidence to routinely support the use of massage therapy in RLS.

7.2.4 Acupuncture

Acupuncture has also been recommended by some as a therapy for RLS. Nonetheless, similar to massage therapy, there is minimal evidence to recommend acupuncture for RLS symptoms. In a Cochrane review, the authors found out of 14 potential studies only 2 met the inclusion criteria to be valid and both trials had methodological and/or reporting issues. Overall, the Cochrane reviewers felt that there was no significant data to support the use of acupuncture in RLS (Cui Y, 2008).

7.2.5 Endovenous laser ablation & sclerotherapy

Recently, Hayes and colleagues have reported on the use of endovenous laser ablation and sclerotherapy for the treatment of RLS. They screened 89 patients for RLS using the 2003 IRLSSG criteria. A total of 35 patients met inclusion criteria with 16 assigned to the control group and 19 to the interventional group. IRLS scores were obtained at baseline and 6 weeks later and showed a significant symptom improvement of 80% in the interventional group. The authors suggest that endovenous laser ablation therapy improves symptoms in RLS patients with superficial venous insufficiency (Hayes CA, 2008). The only other study assessing the efficacy of sclerotherapy in RLS was published by Kanter in 1995. In that paper, 1397 patients presenting to a varicose vein clinic were screened for RLS using an interview and a questionnaire (pre-1995 IRLSSG). Of these, 312 patients (22%) were felt to have RLS with 113 patients receiving treatment with sclerotherapy. The vast majority of patients (98%) reported subjective initial improvement in RLS symptoms although a substantial minority reported recurrent symptoms at 2 year follow-up (Kanter AH, 1995).

8. Conclusion

RLS is a common medical disorder which remains underdiagnosed. The underlying etiology is still not fully elucidated but there is increasing understanding of some mechanisms of disease especially in secondary RLS. Many treatment options are available although issues of augmentation and rebound continue to cause problems with RLS control. It is highly recommended that health care providers be aware of RLS symptoms and recognize the disease in their patients.

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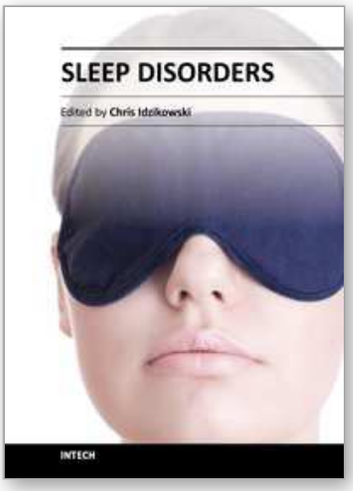

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For progress to be maintained in a clinical field like sleep medicine, unimpeded, unrestricted access to data and the advances in clinical practice should be available. The reason why this book is exciting is that it breaks down the barriers to dissemination of information, providing scientists, physicians, researchers and interested individuals with a valuable insight into the latest diverse developments within the study of sleep disorders. This book is a collection of chapters, which can be viewed as independent units dealing with different aspects and issues connected to sleep disorders, having in common that they reflect leading edge ideas, reflections and observations. The authors take into account the medical and social aspects of sleep-related disorders, concentrating on different focus groups, from adults to pregnant women, adolescents, children and professional workers.

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