Restless Leg Syndrome (RLS): Recent Advances and Future Challenges: A Review

Charan Reddy Kudumula

Department of Internal Medicine, MGM Medical College & Hospital, Kamothe, Navi Mumbai, India

ABSTRACT

Restless legs syndrome (RLS)/Willis-Ekbom disease (WED), or Jimmy Legs is a neurological sensory-motor disorder that causes intense restlessness and unpleasant creepy-crawly feelings inside the lower legs at rest. It can be idiopathic or symptomatic and affects 7–10% of general population with a significant female predominance. RLS is generally associated with conditions like iron deficiency, low serum ferritin levels, pregnancy, menopause, chronic renal disease, diabetes mellitus, cardiovascular disease, Parkinson’s disease and rheumatoid arthritis etc, however, the relationship is not completely understood. The purpose of the review is that in recent years there have been a number of advances in the field of RLS. Here, we present recent advances pertaining to epidemiology, etiology, pathogenesis, diagnosis and practical management of RLS.

Keywords: Periodic limb movements, restless leg syndrome, sleep, dopamine, levodopa, pramipexole, dopamine agonists

Running Title: Recent advances and future challenges in RLS

1. INTRODUCTION

The English physician and Anatomist Sir Thomas Willis made the first known medical
description of Restless Leg Syndrome (RLS) in 1672 [1]. Subsequently, other
descriptions of RLS were published by Dr. Sauvages in 1763 followed by Dr. Tourettein
1898[2,3]. However, it was not until almost three centuries after Thomas 30 Willis work, in
1945 a Swedish neurologist Dr. Ekbom provided a comprehensive report of RLS.
Dr.Ekbom's work was largely ignored, until it was rediscovered by Dr. Walters et al [4].
For the present review, we searched Medline, the Cochrane Library and the National
Institute for Health and Clinical Excellence website with the search term “restless legs
syndrome” and updated the current trends and future research possibilities to tackle RLS.
Furthermore, we also considered evidences from published literature and guidelines on
the diagnosis and treatment of RLS by the International RLS study group, the European
restless legs study group and the movement disorders society taskforces and several
others.
2. CLINICAL FEATURES OF RLS
Restless Legs Syndrome (RLS) or Willis/Wittmaack-Ekbom's Syndrome (WED/RLS) (referred
as RLS), is a rare neurologic disorder that very often goes undiagnosed or
misdiagnosed. RLS is the most common disorder of combined sensory and motor
dysfunction we have ever heard of[5]. Many patients suffer from the symptoms of this
disorder without realizing anything is wrong. In recent years, public and health-care
practitioner awareness of RLS has been increasing considerably, presumably due to the
available of better treatment options [6].
The hallmark of RLS is a marked discomfort in the legs and rarely in arms or elsewhere
typically worse during periods of rest, relaxation or inactivity and symptoms are relieved
by leg movements, stretching, yoga, biking or other physical activity, but not for long.
The terms that patients use to describe the symptoms of RLS include: painful, 'antsy',
electrical shock, insects crawling under the skin, creeping, tingling, pulling, itching, drawing, needle poking and numbness [7,8]. These uncomfortable sensations bring about an often-urgent desire to move the legs. Available literature also revealed a strong circadian influence in RLS, and symptoms are worsened within 15 to 30 minutes of reclining in bed [9,10]. Many patients with RLS complain of difficulty in getting sleep leading to frequent night awakenings, walking and chronic sleep deprivation and stress [11].

3. 59 EPIDEMIOLOGY OF RLS

In the past decade, several studies have been published from different populations examining the prevalence of RLS [8,12]. The exact prevalence of RLS estimation is difficult, because its severity and frequency varies enormously between individual sufferers. However, few epidemiological studies suggest that prevalence of RLS in the general population is 5% and up to 10% of those aged 65 and older [8]. Similar prevalence rates in the general population have been reported in Canada [13]. The prevalence of RLS among Caucasians ranges from 5-15% [14]. RLS can be either primary (idiopathic) or symptomatic (secondary) forms, and start at any age (from childhood to >80 years) [9]. Primary RLS usually begins slowly, before 40–45 years of age and disappear for months or even years, but the cause is unclear. In a survey among members of the Willis-Ekbom Disease Foundation, it has been reported up to 45% of patients had their first symptoms before the age of 20 years.

Some studies have reported that prevalence of RLS is about two times higher in women than in men and it increases with age [15]. One Asian study reported a lower prevalence
of RLS in these populations [14, 16]. In a study of 626 pregnant women admitted to a single center, the prevalence of RLS was 10 % before pregnancy and increased to 30% during pregnancy [17], but exact cause for such an increase is not known, although deficiency of iron/folate, and changes in ovarian hormone levels are responsible to some extent[18]. One of the studies from Sweden revealed that RLS prevalence is about 29.60% in the third trimester pregnancy [19].

4. ETIOLOGY OF RLS

What causes RLS is somewhat a mystery till date, hence its exact etiology is not known in most patients. RLS is a progressive disease for some, while the symptoms may remit in others. Although RLS is generally thought to be a disease of adulthood, it can occur in children, where it is often misdiagnosed as attention deficit hyperactivity disorder (ADHD) [20] growing pains [21] or other sleep disorders [2]. A number of retrospective studies suggest that children and adults with RLS have a relatively high rate of comorbid psychiatric disorders [22]. It has multifactorial etiology and commonly can be drug-induced [23]. It has been demonstrated that the capacity for iron 88 transport to the central nervous system is abnormal in idiopathic RLS [24]. Ferritin levels lower than 50 ng/L (normal range 18.0–300 in men, 18.0–150 in women) correlate significantly with a greater severity of RLS and decreased sleep efficiency [25].

Primary RLS is frequently associated with changes in serum and cerebrospinal fluid (CSF) levels of iron, ferritin and transferrin[26]. These authors have shown that 65 % decrease in cerebrospinal fluid (CSF) ferritin levels and 300% increase in CSF transferrin levels in primary RLS patients. Iron is the most abundant transition metal in the human brain, and ferritin is the main iron storage protein in this organ. Tyrosine
hydroxylase, the key enzyme in dopamine synthesis, require iron as a co-factor, therefore iron deficiency may affect dopamine production, and lack of synthesis of dopamine due to malfunction of brain cells known to promote RLS symptoms [27]. Secondary RLS often has a sudden onset after age of 40 and can develop in about 30% of the individuals with conditions such as rheumatoid arthritis [28], renal failure [29], gastric surgery [30], diabetes mellitus [31], use of certain drugs and frequent blood donations [32]. Family history consistent with autosomal dominant inheritance [33,34] and recessive modes of inheritance [35] are known to present in more than 60% of primary RLS patients [36].

6. PERIODIC LIMB MOVEMENTS OF SLEEP DISORDERS (PLMS/PLMD)

RLS is commonly associated with sleep disturbance with highly stereotyped, involuntary, uncontrollably twitch or jerking movements typically involve extension of the big toe with partial flexion of the ankle, knee and hip during sleep known as periodic limb movements of sleep (PLMS). Each movement lasts approximately 0.5 to 5 seconds and is repeated every 20 to 40 seconds, leaving the affected patient fatigued the following day [37]. PLMS also called as nocturnal myoclonus [38] is found in 30% of individuals aged 50–65 years and in 45% of individuals over 65 years [37]. PLMS itself is not diagnostic of RLS nonetheless, a high PLMS index serves as a sensitive and specific diagnostic marker for RLS [39]. When sleep deprivation and daytime fatigue co-exist with PLMS, the term periodic limb movement disorder (PLMD) is used. More than 80% of the older age people with RLS also experience PLMD. Unlike RLS, whose diagnosis is clinically based, PLMD diagnosis is based on combined complaints like disturbed sleep, daytime fatigue and limb movements [40].
7. RLS: INDIAN PERSPECTIVE

RLS is a hardly studied, probably under-diagnosed condition in India [41]. The incidence in India has been reported to be much less as compared to the Western countries. Only the hospital-based data has been reported in Indian literature and population-based literature is scanty. The first Indian population study on RLS showed prevalence about 2.1% in Southern India [42]. These authors further stated that the incidence of RLS in normal subjects as 6.25% and 34.37% in anemic patients. RLS is likely associated with conditions like chronic menorrhagia and repeated (> 5 times) blood donations/year [42]. The incidence of RLS has been reported to be 1.5 - 6.6% in patients of chronic renal failure and 9.5% in patients with sleep disorders [43].

8. RLS: PREGNANCY AND MENOPAUSE

RLS is about twice as common in pregnant women than in the overall population. If RLS existed before pregnancy, with no other condition, the symptom intensity often increases during pregnancy, especially in the last trimester, with severity peaking during the last weeks before parturition, but the mechanism by which pregnancy worsens RLS is yet to be known. Additionally, primary RLS is more common in pregnant women with higher estrogen levels than in pregnant women with lower levels [18, 26, 44]. It is not known whether women with RLS during pregnancy have a higher risk of prenatal or postpartum depression. In women, during the menopausal transition, estrogen and progesterone influence development of RLS. In fact, an increased prevalence of primary RLS has been found in periods of higher estrogen levels [45]. When RLS arises de
novo during pregnancy, usually disappears quickly after childbirth [45].

RLS during pregnancy has the same symptomatology as RLS outside the childbearing period. However, because pregnancy itself often results in sleep problems, it is difficult to say how much effect of RLS per se has in this context. Women who have given birth to one or several children have a higher risk of developing RLS, whereas nulliparas have a risk equal to that of men [46]. Available epidemiological data have been unable to clarify whether menopausal symptoms and/or associated decreased levels of ovarian hormones such as estradiol contribute to the increased prevalence of RLS [45, 47]. In general, RLS during pregnancy is treated pharmacologically only if the symptoms are of such difficulty that therapy is inevitable. If a pregnant RLS patient shows an iron deficiency or low serum ferritin level, then intravenous iron preparations may be beneficial [48]. Intravenous iron does not cross the placenta [49], and it is approved for use even during the first trimester of pregnancy.

9. GENETICS OF RLS

As RLS seems to run in families, there could be a genetic factor according to the National Institute of Neurological Disorders and Stroke (NINDS). Clinical surveys have shown that at least 60% of individuals with primary RLS reported a positive family history [50,51]. **Ethnic variations in the prevalence of RLS cannot be ignored given the large influence of genetics in RLS.** Most of the epidemiological studies till date, suggests high prevalence in Northern and Southern Europeans and Northern Americans than in Africans, Middle Eastern, Asians and Hispanics due to different genetic or environmental factors, including nutrition [52]. Although, the familial forms cannot be differentiated easily from the symptomatic forms, it has been suggested that there is an
earlier age of onset and more frequent worsening in patients with hereditary RLS [8]. RLS is 3–5 times greater amongst first degree relatives of subjects suffering from RLS than in subjects without RLS (9 Allen et al, 2003). RLS occurs in nearly 2% of school age children [53] and half of these cases have a positive parental history of RLS [54]. The syndrome is probably underdiagnosed in children, given that 38% of adults have reported the onset of symptoms before age of 20 years and 10% before age of 10 years. Roughly 65% of RLS patients, especially those with an early onset of symptoms, have at least one first-degree relative with the disease [33]. The concordance rate between monozygotic twins also has been reported to be high [53].

RLS is not caused by a single gene defect, but rather is a complex disorder influenced by many genetic and environmental factors, with age being the strongest risk factor [55]. Genome-wide association studies (GWAS) with RLS have demonstrated that primary RLS-associated variant is located on a non-coding region (intron-8) of the MEIS1 gene (2p14). MEIS1 belongs to the TALE family of homeobox (homeopathic box?) transcription factors involved in the development of various organ and maintenance [56]. However, causal single nucleotide polymorphisms (SNPs) and their functional relevance in RLS pathogenesis has remained unknown. It has been shown that non-coding region of MEIS1 appears to be active only during early brain development, associated with aging and have fetal origins [57]. These authors further showed reduced expression of MEIS1 through intronic cis-regulatory element(s) predispose to RLS. Mice with reduced MEIS1 mRNA and protein expression display hyperactivity, which resembles the human condition of RLS. It is of interest to know how variants contribute to RLS as they often lie in noncoding regions of the genome [58].

In a genome-wide study involving 401 subjects with RLS and 1644 controls, all of
European origin, RLS haplotype risk reported to be associated with six genetic loci (12q, 14q, 9p, 20p, 2q and 16p) encompassing the nitric oxide synthase-1 (NOS1), MEIS1, BTBD9, MAP2K5, SKOR1 and protein tyrosine phosphatase receptor type-D (PTPRD) genes [51, 53, 55, 57, 59-61]. The first genetic locus was discovered in one large French-Canadian family and maps to chromosome 12q [35]. The second RLS locus maps to chromosome 14q and was discovered in one Italian family [34]. The third RLS locus maps to chromosome 9p and identified in two unrelated American families [50]. The fourth RLS locus maps to chromosome 20p and was also identified in a large French-Canadian family with RLS. The fifth RLS locus maps to chromosome 2q and was found in three related families in South Tyrol [60]. The sixth RLS locus maps to chromosome 16q and was found in one French-Canadian family [55].

10. IMPACT OF RLS ON HEALTH RELATED AND QUALITY OF LIFE (HRQOL)

RLS is a common sensorimotor disorder and has a significant impact on quality of life. In literature databases, several prevalence studies were found concerning RLS and health related quality of life (HRQOL). Many people with RLS say that their job, personal relations and activities of daily living are strongly affected as a result of their exhaustion. They are often unable to concentrate, have impaired memory or fail to accomplish daily tasks [62]. These authors further reported that, RLS-positive women had an impaired mental health related quality of life (HRQOL) as compared to RLS-negative women and more often suffered from comorbidities. In a study by McDonagh and group [63] revealed that RLS was detected in about 36% of patients attending a phlebology (vein disease) clinic, compared to 18% in a control group. RLS occur frequently in people with folate deficiency, magnesium deficiency, pregnancy and menopause [64]. In some people, use
of certain medicines like calcium channel blockers, lithium and neuroleptics cause RLS.

Several observational studies have indicated a higher than expected incidence of RLS in people suffering from various health issues such as chronic renal disease [65], varicose vein [63], erectile dysfunction [66], fibromyalgia [67], diabetes mellitus [68], depression [19], peripheral neuropathy [69], metabolic dysregulation [70], cardiovascular disease [71], migraine [72], impaired glucose tolerance [73], body mass index (BMI) [74, 75], decreased lung function [76] and Parkinson's disease [77].

Emerging evidence also suggests that RLS is associated with certain auto-immune Disorders like Sjögren's syndrome [78], systemic lupus erythematosus (SLE) [79], rheumatoid arthritis [80], and Multiple sclerosis [81]. However, the exact association between RLS and these disorders is yet to be elucidated. Some of the key disorders associated with RLS are discussed below.

(a). Depression: Many studies have shown strong association between depression and RLS [19, 82]. RLS is a disorder known to be associated with nervous system, and often misdiagnosed for mood disorder or any other neurological disorder. Diagnosis of mood disorders in patients with RLS is complicated by overlapping symptoms. Fatigue, sleep disturbance, diminished concentration and psychomotor agitation are common to both RLS and depressive disorders [12]. Pain and social isolation are also predictors for depression, and these symptoms are frequently observed in people with RLS [82]. Both RLS and depression appear to be involved disturbances in the dopaminergic neurotransmitter system [12] (Becker and Novak 2014). Treatment of co-morbid depression in patients with RLS should be cautious, since anti-depressants can aggravate RLS symptoms.

(b). Cardiovascular Disease: The potential mechanisms for an association between RLS and cardiovascular disease (CVD) have been reported in recent studies [71, 83]. Richy et al [84] have reported from a two-year retrospective cohort study that patients develop cardiac dysrhythmias and stroke after an initial diagnosis of RLS.
In a Swedish study, male RLS subjects more often suffered from heart problems, and an association was shown between RLS and hypertension related cardiac problems [85]. Recent studies have also indicated that men with heart failure and a PLMS index >5 events/hr had a higher mortality rate than men without this disorder [86, 87]. Though, most of the studies supported the relationship between RLS and CVD, further investigations are essential to decipher the molecular mechanism in this association.

(c). Erectile dysfunction: Men with restless leg syndrome are more likely to have erectile dysfunction (ED), new research suggests, but it's not clear which one comes first, and how the two conditions are related [66]. In a six years of follow-up study initiated in 2002 with >11,000 men (mean age 64 years) who were free of ED, diabetes, and arthritis when they were enrolled, have revealed that men with at least 5 and 14 episodes of RLS each month were about 50 and 66% higher risk of developing ED respectively than men without this disorder, even after ruling out the effect of factors known to increase the risk of ED such as age, smoking, diabetes, and antidepressant medications [66]. The culprit could be the dopamine, a neurotransmitter in the brain that plays a role in both RLS and ED [88]. Dopamine helps to relax the muscles of the penis, leading to an erection and many researchers believe that proper transmission of dopamine signals from the brain is essential to avoid RLS symptoms [27, 89].

12. RLS: THE DIAGNOSTIC CRITERIA

RLS is generally a life-long condition for which there is no cure. RLS is frequently unrecognized in medical practice largely due to comorbidities that can mimic its symptoms [12]. Diagnosis of RLS is purely based on clinical symptoms and there is no specific test available [90]. During clinical based diagnosis of RLS, generally physicians...
ask patients five questions established by the International RLS Study Group in 2012[91]. These queries are: (1) Is there an overwhelming urge to move lower and/or upper limb/s? (2) Do the unpleasant sensations or urge to move legs begin or worsen during rest or inactivity? (3) Are these symptoms relieved by movement of legs such as walking or stretching? (4) Do the symptoms worsen in the evening or night than during the day or only occur in the evening or night? (5) Are the symptoms not solely accounted for by another medical or behavioral condition, such as leg cramps or habitual foot tapping?.

The diagnosis of RLS is definitely a problematic, because patients typically present with disturbed sleep, discomfort, pain or a non-specific increase in motor activity. In a recent report by Johns Hopkins University School of medicine revealed that the neurotransmitter, glutamate levels were found to be abnormally high levels in RLS subjects as compared to controls. The higher the level of glutamate in the brain of those subjects with RLS, the worse the sleep [92]. RLS can be confused with a variety of conditions like spinocerebellar atrophy, peripheral neuropathy, spinal canal stenosis, lumbosacral radiculopathy, myelopathy and leg cramps, etc [93]. Moreover, in subjects with comorbidities like liver disease, chronic inflammation, CVD, diabetes, low physical activity [87] or malignancy, the serum ferritin levels known to be increased as an acute phase reactant, in which case additional serum iron studies are necessary to evaluate for iron deficiency. Though the pathophysiological association between iron deficiency and RLS is not well understood, iron supplementation is recommend, if ferritin levels are below 50 μg/L[94].
Recent studies provided insights into the pathophysiology of RLS and management strategies [95]. Here, we mention two long-standing issues in the treatment of RLS. First and foremost issue is that, since the primary RLS being strictly a dopaminergic process, therefore dopaminergic agents may be considered as treatment option. The second and equally important issue is drug-induced progressive symptomatic worsening of RLS, and it is the leading cause of the failure of dopaminergic agents, which have been recognized as such for nearly two decades [12]. Some of the recent advances in the treatment of RLS are summarized below.

(a) Non-pharmacological treatment
Since the cause is unknown, it is necessary to identify the symptoms for choosing treatment strategy to relieve the pain. Not all patients need treatment, and only about 20% require either non-pharmacological or pharmacological treatment. Non-pharmacological based measures include certain lifestyle changes such as regular sleep habits, relaxation techniques, moderate regular exercise, yoga and meditation or other ways to ease tension during the day can help to cope with the condition and ease symptoms. Muscles relax with gentle stretches, massage and warm baths can also ease the pain. It is better to void caffeine, alcohol and tobacco as they can make RLS symptoms worse [12].

(b) Pharmacological treatment
For pharmacological treatment, several drugs including dopaminergic agents, opioids, benzodiazepines (nervous system depressants), anti-convulsants, iron, adenosine, adrenergic drugs, magnesium and several other drugs are available. Akpinar [96] reported the impact that levodopa (L-DOPA) had on RLS symptoms, thus began the
dominance of dopamine drugs as the primary treatment option for RLS. An important side effect of L-DOPA, which limits its use, is augmentation in 70% of patients and the risk increases with higher doses [97]. It has been shown that dopamine antagonist, carbidopa that cross the blood–brain barrier, aggravate features of RLS by preventing the peripheral conversion of L-DOPA to dopamine. As a result, more L-DOPA is available to cross the blood–brain barrier [98].

(i). Dopaminergic agonists

Although, dopaminergic agonists are considered the first-line pharmacological therapy for RLS, most of them are associated with worsening of the disease due to longer onset of action than L-DOPA [12]. L-DOPA agonists including pergolide, pramipexole, andropinrole (Requip) were preferred over other medications. Ropinirole was the first approved medication to receive the US Food and Drug Administration (FDA) approval in 2005 to treat moderate to severe RLS.

Among non-ergot derived compounds, pramipexole (Mirapex) is favored over ropinirole [7] and recommended for long-term use in view of good efficacy, superior response and fewer adverse effects [12]. Several major pharmaceutical companies have been reported marketing drugs without an explicit approval for RLS, which are "off-label" applications for drugs approved for other diseases. Quinine is frequently used off-label drug to treat RLS but is not recommended by the FDA due to serious hematological side effects. Recently, it has been showed that expensive pregabalin (Lyrica) recommended to treat nerve pain and seizures (not FDA-approved for the treatment of RLS) was effective in reducing RLS symptoms than pramipexole [99]. However, six of the patients who had taken pregabalin had suicidal thoughts. Whether pregabalin positive effects will be sustained without undesirable side effects and whether the
treatment will improve the quality of life are some of the questions that need to be addressed by conducting long term clinical trials.

The ergot derived dopamine agonists such as piribedil, cabergoline, bromocriptine and pergolide are used for the treatment of RLS. Adverse symptoms include pulmonary fibrosis, insomnia, dyspepsia, nausea, headache, rhinitis and cardiac dysfunction have made treatment of pergolide obsolete [100]. A 24hrs transdermal patch using rotigotine (RTG) was reintroduced to the U.S market in mid-2012, after FDA approval to relieve both night and day time symptoms for patients who have not responded to other treatments [101]. This may have a great potential to alleviate many of the difficulties associated with dosing patients with RLS. In clinical practice, iron 346 supplementation would be recommended if the patient had ferritin levels ≤50 μg/L. If the ferritin is above this value, physician prefers to prescribe with one of the dopamine agonists.

(ii). Anti-epileptic drugs (anti-convulsants)

Several oral anti-convulsant drugs such as gabapentin enacarbil (Neurontin or Horizant), carbamazepine and valproic acid have been tried for the treatment of painful RLS [102]. Because of their hypnotic effects, these drugs are useful to treat sleep onset insomnia due to RLS. Gabapentin enacarbil is the favored treatment for patients who cannot tolerate dopaminergic drugs. Amongst the benzodiazepines, clonazepam is frequently used medication for RLS. It works mainly on the quality of sleep, and not on the pathology of RLS [12].

(iii). Opioids and opioid-agonists: Opioids are often used for RLS, but the evidence to support their effectiveness is not robust due to lack of large scale clinic trials. Moreover, the use of opiates for RLS has not been given the same level of financial support to conduct large scale clinical trials as dopamine drugs. The doses of dopaminergic drugs,
opioids and their agonists, anti-epileptic recommended for RLS treatment and their
common adverse symptoms are listed (Table-1).

14. CONCLUSIONS AND FUTURE DIRECTIONS

No one knows exactly what causes RLS and no known cure for RLS, nor is there one
drug which works for everybody. We have some idea about the cause of RLS, but we
have miles and miles left behind before we reach a level of understanding of RLS and
miles more again before we will be able to predict or prevent its occurrence. Physicians
suggest certain lifestyle changes and activities to reduce adverse symptoms or they
suggest a variety of appropriate medications, which includes non-ergot dopamine
agonists (pramipexole, ropinirole, and rotigotine) and calcium channel-α2-delta ligands
(gabapentin enacarbil and pregabalin) and rotigotine for treating moderate to severe RLS.
Although, several issues have been clarified, many gaps still exist particularly in the
identification of reversible contributing factors and use of appropriate pharmacological
drugs for the treatment of RLS. Despite difficulties in differential diagnosis, correct
identification and management are critical to prevent clinical consequences of RLS.
Given the impact of RLS on the psychological well-being of subjects, further studies in
this direction would not only help in relieving adverse RLS symptoms, but also reduce
depressive symptomatology. Moreover, there are no established guidelines regarding
clinical trials for RLS, large scale trials with longer follow-up periods for different drugs
are need of the hour. We believe this will encourage scientists to develop safe and
effective drug for this common but uncommonly diagnosed syndrome. If the recent
developments in this important area stand the test of time, one of the possible causes of
RLS could be suggested and investigated.

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4 Temazepam 0.10-.50 1-3 nausea, fatigue, somnolence, headache

5 Clonazepam 5-50 100 - 400 sedation, tolerance

Eszopiclone

6 Valproic acid 100-300 1,000 - 3,000 dizziness, Increase in body weight, 25
tremor, fatigue and hair loss

Table 1. Pharmacological therapy to relieve from RLS symptoms [682 12, 98, 99, 101,102

III Dopamine precursors - - -

1 Levodopa (+ carbidopa or benserazide)
20-50 100-200 nausea, vomiting, orthostatic hypotension, hallucination,
augmentation of symptoms,
insomnia

IV Low potency opioids/
Non-ergot dopamine agonists

1 Pramipexole 0.125–1 1.50-3.0 nausea, fatigue, somnolence, headache, augmentation

2 Ropinirole 0.25 0.5–3.0 impulse control disorders hypotension, nausea

3 Rotigotine patch 0.5-1 1–3.0 skin reactions

4 Morphine 2.5-5 30-45 nausea, somnolence
5 Propoxyphene 50-100 400 -600 nausea, depression

6 Pergolide 0.025 0.50-1 risk of valvular heart disease and retro-peritoneal or pleuropulmonary fibrosis

7 Oxycodone 2.50-5.0 20-30 dyspepsia, nausea, headache, rhinitis and cardiac dysfunction

8 Codeine 2.50-5 30-60 nausea, sedation and respiratory depression

9 Hydrocodone or Methadone 1 -2.5 5.0-20 constipation, nausea, dizziness, sedation and potential for drug addiction / tolerance

**NOTICE:** The blue and highlighted words or letters have been added to the text where necessary. The red and highlighted words or letters are suggested to be deleted from the text.