



# Clinical Characteristics and Pathophysiological Features of Restless Legs Syndrome (RLS): Recent Advances and Future Challenges

K. V. Charan Reddy<sup>1\*</sup>

<sup>1</sup>Department of Internal Medicine, MGM Medical College & Hospital, Kamothe, Navi Mumbai, India.

## Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

## Article Information

DOI:10.9734/BJMMR/2015/14009

### Editor(s):

(1) Ricardo Forastiero, Professor of Physiology and Internal Medicine, Haematology, Favaloro University, Argentina.

### Reviewers:

(1) Anonymous, Brigham Young University, USA.

(2) Seyedaghanoor Sadeghi, Medical Doctor and Professional Homeopathy, Formal Member of LMHI, Tehran, Iran.

(3) Sujith Ovallath, Head of Neurology and Director James Parkinson's Movement Disorder Research Centre, Kannur Medical college, Kerala, India.

Complete Peer review History: <http://www.sciencedomain.org/review-history.php?iid=719&id=12&aid=6964>

**Review Article**

**Received 15<sup>th</sup> September 2014**

**Accepted 29<sup>th</sup> October 2014**

**Published 15<sup>th</sup> November 2014**

## ABSTRACT

Restless Legs Syndrome (RLS)/Willi's-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 primary (idiopathic) or secondary (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. In this review, I discussed recent developments on epidemiology, etiology, pathogenesis, diagnosis and clinical management of RLS.

**Keywords:** *Periodic limb movements; restless legs syndrome; sleep; dopamine; levodopa; pramipexole; dopamine agonists.*

\*Corresponding author: Email: [chnr@rediffmail.com](mailto:chnr@rediffmail.com);

## 1. INTRODUCTION

The English physician and Anatomist Sir Thomas Willis made the first known medical description of Restless Legs Syndrome (RLS) in 1672 [1]. Subsequently, other descriptions of RLS were published by French neurologists Prof. Boissier in 1763 followed by Prof. Tourette in 1898 [2,3]. However, it was not until almost three centuries after Thomas Willis's work, in 1945 a Swedish neurologist, Prof. Wittmaack provided a comprehensive report of RLS. Prof. Wittmaack work was largely ignored, until it was rediscovered by Prof. Walters's group [4]. For the present review, I 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 address various issues of RLS. Furthermore, I 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 to RLS), is a neurologic disorder that very often goes undiagnosed or misdiagnosed. RLS is the most common disorder of combined sensory and motor dysfunction we have never heard of [5]. In recent years, public and health-care practitioners' awareness of RLS has considerably increased due to the availability 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 legs movement, 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 legs. Available literature revealed that a strong circadian influence in RLS, indicating a worsening of symptoms 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, having to walk at night and chronic sleep deprivation and stress [11].

## 3. EPIDIMIOLOGY OF RLS

In the past decade, several studies published from different populations examining the prevalence of RLS [8,12]. The exact prevalence of RLS is difficult to find out, 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 age 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 45 years of age and disappear for months or even years. In a survey among members of the Willis-Ekbom Disease Foundation, it was shown that 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 revealed that lower prevalence of RLS in their populations [16]. One of the studies from Sweden revealed that RLS prevalence is about 29.60% in the third trimester pregnancy [17]. 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 [18]. However, the exact cause for such an elevation is currently not known, although deficiency of iron/folate and changes in ovarian hormone levels are responsible to some extent [19].

## 4. ETIOLOGY OF RLS

What causes RLS is somewhat a mystery to date; hence its exact etiology is unknown in most patients. 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 seems to have a multifactorial etiology and commonly can

be drug-induced [23]. It was shown that the capacity for iron transport to the central nervous system (CNS) is abnormal in idiopathic RLS cases [24]. Moreover, in subjects with comorbidities like liver disease, chronic inflammation, CVD, diabetes, low physical activity and malignancy, the serum levels of ferritin are reported to be increased as an acute phase reactant [25]. Though, the pathophysiological association between iron deficiency and RLS is not well understood, iron supplementation is recommended, if ferritin levels are below 50 µg/L [26]. 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 [27].

Two subgroups of RLS phenotypes have been identified with regard to age of onset, primary (idiopathic) and secondary (symptomatic) RLS. Patients with an onset of primary RLS before the age of 45 were found to have a significantly higher incidence of affected relatives compared with those who reported symptoms onset later in life [28]. Primary RLS is frequently associated with decrease in cerebrospinal fluid (CSF) levels of ferritin and transferrin by 65% and increase transferrin levels by 300% [29]. Iron is the most abundant transition metal and ferritin is the main iron storage protein in human brain. Tyrosine hydroxylase, the key enzyme in dopamine synthesis, require iron as a co-factor, therefore iron deficiency may affect dopamine synthesis due to malfunction of brain cells that promote RLS [30].

Secondary RLS may occur after the age of 40-45 and can develop in about 30% of individuals with conditions such as fibromyalgia and rheumatoid arthritis [31]. There are many causes of secondary RLS, which includes renal failure [32], Iron deficiency, pregnancy, gastric surgery [33], diabetes mellitus [34], use of certain drugs and frequent blood donations [35]. Family history consistent with autosomal dominant inheritance [36,37] and recessive modes of inheritance [38] are known to present in more than 60% of secondary RLS patients [39].

## **5. PERIODIC LIMB MOVEMENTS OF SLEEP DISORDERS (PLMS/PLMD)**

RLS is commonly associated with sleep disturbance with highly stereotyped, involuntary, uncontrollably twitch or jerking movements that 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 [40]. PLMS also called as nocturnal myoclonus [41], is found in 30% of individuals aged 50–65 years and in 45% of individuals over 65 years [40]. PLMS itself is not diagnostic of RLS. Nonetheless, a high PLMS index serve as a sensitive and specific diagnostic marker for RLS [42]. 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 clinically based, PLMD diagnosis is based on combined complaints like disturbed sleep, daytime fatigue and limb movements [43].

## **6. RLS: INDIAN PERSPECTIVE**

RLS is a hardly studied, probably under-diagnosed condition in India [44]. 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 scant. The first prevalence study on RLS reported to be 6.25% in general population and 34.37% in anemic patients [45] in Southern India. RLS is associated with conditions like chronic menorrhagia and repeated blood donations (> 5 times/year) [45]. The incidence of RLS shown to be 1.5 - 6.6% and 9.5-12.4% in patients suffering from chronic renal failure and sleep disorder respectively [46].

## **7. 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 complication, the symptom intensity often increased during pregnancy, especially in the last trimester before parturition [18]. However, the mechanism by which pregnancy worsen RLS is yet to be known. Primary RLS is more common in pregnant women with higher estrogen levels than in pregnant women with lower levels [18,47]. It is not known whether women with RLS during pregnancy have a higher risk of prepartum or postpartum depression. In women, during the menopausal transition, estrogen and progesterone levels influence the development of RLS. An increased prevalence of primary RLS

has been reported in periods of higher estrogen levels [48]. When RLS arises *de novo* during pregnancy, usually disappears quickly after childbirth [48].

RLS during pregnancy has the same symptomatology as RLS outside the child bearing 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 [49]. Available epidemiological data is unable to clarify whether menopausal symptoms and/or associated decreased levels of ovarian hormones contribute to the increased prevalence of RLS [48,50]. 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 [51]. Intravenous iron does not cross the placenta [52], and it is approved for use even during the first trimester of pregnancy.

## 8. 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 [53,54]. Most of the epidemiological studies to date, suggest 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 [55]. 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]. RLS occurs in nearly 2% of school age children [56] and half of these cases have a positive parental history of RLS [55]. The syndrome is probably under diagnosed in children, given that 38% of adults have reported the onset of symptoms before age of 20 and 10% before age of 10. Roughly 65% of RLS patients, especially those with an early onset of symptoms

have at least one first-degree relative with the disease [36]. The concordance rate between monozygotic twins also has been reported to be high [56].

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 [57]. 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 transcription factors involved in the development of and maintenance of various organs [58]. However, causal single nucleotide polymorphisms (SNPs) and their functional relevance in RLS pathogenesis have remained unknown. It has been shown that non-coding region of MEIS1 appears to be active only during early brain development may be associated with aging and has fetal origins [59]. In the same study, it was also shown that reduced expression of MEIS1 through intronic cis-regulatory element (s) predisposes to RLS. Mice with reduced MEIS1 mRNA and protein expression display hyperactivity, which resembles the human condition of RLS [60]. It is of interest to know how variants contribute to RLS as they often lie in non-coding regions of the genome.

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 [55,56,58,60,61-64]. The first genetic locus was discovered in one large French-Canadian family and maps to chromosome 12q [38]. The second RLS locus maps to chromosome 14q and was discovered in one Italian family [37]. The third RLS locus maps to chromosome 9p and identified in two unrelated American families [53]. 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 [63]. The sixth RLS locus maps to chromosome 16q and found in French-Canadian family [58].

## **9. IMPACT OF RLS ON HEALTH RELATED 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 personal relations with their family have strongly affected as a result of their exhaustion, are often unable to concentrate, had an impaired mental HRQOL or fail to accomplish daily tasks and more often suffered from comorbidities [65]. A study by McDonagh et al [66] revealed RLS was detected in about 36% of patients attending a phlebology (vein disease) clinic as compared to 18% in control group. RLS occurs more in people with folate deficiency, magnesium deficiency during pregnancy and menopause [67]. 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 [68], varicose vein [66], erectile dysfunction [69] fibromyalgia [70], diabetes mellitus [71], depression [19], peripheral neuropathy [72], metabolic dysregulation [73], cardiovascular disease [74], migraine [75], impaired glucose tolerance [76], body mass index (BMI) [77,78], decreased lung function [79] and Parkinson's disease [80]. Emerging evidence suggests that RLS is associated with certain auto-immune disorders like Sjögren's syndrome [81], Systemic Lupus erythematosus (SLE) [82], Rheumatoid arthritis [83] and Multiple sclerosis [84]. 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.

### **9.1 Depression**

Many studies have shown strong association between depression and RLS [19,85]. 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 [85].

Both RLS and depression appear to be involved disturbances in the dopaminergic neurotransmitter system [12]. Treatment of co-morbid depression in patients with RLS should be cautious, since anti-depressants can aggravate RLS symptoms.

### **9.2 Cardiovascular Disease**

The potential mechanisms for an association between RLS and cardiovascular disease (CVD) have been reported in recent studies [71,86,87]. Richey et al. [87] have demonstrated that from a two-year retrospective cohort study, those 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 [88]. Recent studies have also indicated those men with heart failure and a PLMS index >5 events / hr had a higher mortality rate than men without this disorder [89]. Though, most of the studies supported the relationship between RLS and CVD, further investigations are necessary to decipher the molecular mechanism of this association.

### **9.3 Erectile Dysfunction**

Men with RLS are more likely to have erectile dysfunction (ED) a new research suggests. However, it is unclear which one comes first and how the two conditions are related to each [69]. In a six year 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 at 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 [90]. The culprit could be dopamine, a neurotransmitter in the brain that plays a critical role in both RLS and ED [91]. 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 [30,91].

## **10. RLS: 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 co-morbidities that can mimic its symptoms [12]. Diagnosis of

RLS is purely based on clinical symptoms and there is no specific test available [92]. During clinical based diagnosis of RLS, generally physicians ask patients five standard questions established by the International RLS Study Group in 2012 [93]. These queries are: (1) Are there an over whelming 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 having to walk at night 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 these symptoms are not solely accounted for by another medical or behavioral condition such as legs cramps or habitual foot tapping?

The diagnosis of RLS is definitely problematic, because patients typically present with disturbed sleep, discomfort, pain or a non-specific increase in motor activity. A recent report by Johns Hopkins University School of medicine revealed that the levels of neurotransmitter, glutamate were found to be abnormally high in RLS subjects as compared to controls. Higher the levels of brain glutamate in those subjects with RLS worse the sleep [94]. RLS can be confused with a variety of conditions like spino-cerebellar atrophy, peripheral neuropathy, spinal canal stenosis, lumbosacral radiculopathy and myelopathy etc, [95].

## **11. RLS: PATHOPHYSIOLOGY AND MANAGEMENT STRATEGIES**

The pathophysiology of RLS is not clear. Recent studies provided insights into the pathophysiology of RLS and its management strategies [96]. Here, we mention two long-standing issues in the treatment of RLS. First and foremost issue is that, primary RLS appears to be dopaminergic process, hence dopaminergic drugs may be considered as primary treatment option. The second and equally important issue is the 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 important studies in the treatment of RLS are discussed below.

### **11.1 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. Physical activity and exercise have long been considered as major non-pharmacological treatment options available to RLS sufferers [97]. Mental activities such as reading, prayer, meditation, music, card games, or computer work have been suggested to be successful in decreasing RLS symptoms [97,98]. Other non-pharmacological based measures including certain lifestyle modifications like regular sleep habits, relaxation techniques and yoga or other ways to ease tension during the day can help to cope with the condition and ease symptoms. Muscles relax with gentle stretches 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]. Acupuncture is an ancient Chinese medical therapy is being used in the treatment of RLS [99]. Enhanced external counter pulsation (EECP), massage or hot baths may also ease symptoms associated with RLS [100]. Vibratory stimulation pads have also been shown to improve sleep to a greater extent in patients with moderately severe RLS and is as effective as FDA-approved RLS drugs [101]. Epidemiologic evidence indicates that lack of exercise is a strong predictor of and a significant risk factor for RLS [102]. However, the efficacy of some of these options has not been well documented.

In view of the above, other promising alternative treatment choices are being developed to get relief from RLS. One of them is Near-Infrared Light (NIR) treatment, which is already been on the market, but is currently being used for disorders like neuropathy to increase sensation and reduce nerve pain. Treatment with NIR has been shown to increase blood flow due to its ability to generate bioavailability of nitric oxide (NO) in the endothelium, which through a cascade of events leads to vasodilation [103]. Vasodilation is also the result of exercise, is one of the few non-drug related treatment options that decreases RLS symptoms. While no direct relationship between NO and RLS symptoms have been shown, it is plausible that this radical, generated in the lumen of blood vessels might have similar benefits to the patients as exercise. Further research into this hypothesis need to be established. Randomized clinical trial would shed more light on the usefulness of this treatment.

### **11.2 Pharmacological Treatment**

Until May 2005 there were no US Food and Drug Administration (FDA) approved drugs on the

market for the treatment of RLS. However, later several drugs namely, dopaminergic agents, opioids, benzodiazepines (nervous system depressants), anti-convulsants, adrenergic drugs, magnesium, iron, adenosine and several other drugs are available. Akpinar [104] had reported that the impact that levodopa (L-DOPA) had on RLS symptoms thus began the dominance of dopamine drugs as the primary treatment option for RLS. The side effect of L-DOPA is augmentation in 70% of patients and the risk increases with higher doses, which limits its use [105]. 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 [106].

### **11.2.1 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 and ropinirole (Requip) were preferred over other medications. Ropinirole was the first approved medication to receive the 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 to market drugs without an explicit approval for RLS as an "off-label" drugs approved for other diseases. Quinine is frequently used labeled drug to treat RLS but is not recommended by the FDA due to serious hematological side effects. Recently, it was shown that expensive pregabalin (Lyrica) recommended treating nerve pain and seizures (not FDA-approved for the treatment of RLS) were effective in reducing RLS symptoms than pramipexole [107]. 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 pramipexole, 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 [108]. A 24 hrs 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 [109]. This may have a great potential to alleviate many of the difficulties associated with dosing patients with RLS. In clinical practice, iron supplementation would be recommended if the patient had ferritin levels  $\leq 50$   $\mu\text{g/L}$ . If the ferritin is above this value, physician prefers to prescribe with one of the dopamine agonists.

### **11.2.2 Anti-epileptic drugs (anti-convulsants)**

Several oral anti-convulsant drugs such as gabapentin, pregabalin (Neurontin or Horizant), carbamazepine and valproic acid have been tried for the treatment of painful RLS [110]. Because of their hypnotic effects, these drugs are useful to treat sleep onset insomnia due to RLS. Gabapentin, pregabalin 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].

### **11.2.3 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 clinical 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).

**Table 1. Pharmacological therapy to relieve from RLS symptoms [12,106,107,109,110]**

Sl. no.	Drug	Initial daily dose (mgs)	Daily dose range(mgs)	Side effects
I	<b>Non-dopaminergic medications (Calcium channel <math>\alpha 2\delta</math> ligand)</b>	-	-	-
1	GABA analogues a).Gabapentin enacarbil	50-200	600–1500	sedation, sleepiness, ataxia dizziness, fatigue
	b). Pregabalin	1-5	100–300	somnolence, dizziness, depression
	c).Gabapentin	25 -50	300–1200	weight gain and suicidal ideation reported with pregabalin
II	<b>Benzodiazepines / bezodi-azepine agonists</b>	-	-	-
1	zalepon	2-5	10.0- 20.0	night falls in elderly people, hangover the following day and habituation
2	Carbamazepin	50	100-400	morning drowsiness, dizziness
3	zolpidem	1.5-2.50	5–10	dizziness,
4	Temazepam (Restoril)	0.10-.50	1-3	nausea, fatigue, somnolence, headache
5	Clonazepam	0.1 - 0.25	1 – 2	sedation, tolerance
	Eszopiclone (Lunesta)	0.25-0.50	1.0-2.0	unpleasant taste, headache, drowsiness, infections, dizziness, dry mouth, rash, anxiety, hallucinations
6	Valproic acid	50-100	250 - 500	dizziness, Increase in body weight, tremor, fatigue and hair loss
III	<b>Dopamine precursors</b>	-	-	-
1	Levodopa (+ carbidopa or benserazide)	20-50	100-200	nausea, vomiting, orthostatic hypotension, hallucination, augmentation of symptoms, insomnia
IV	<b>Low potency opioids / Non-ergot dopamine agonists</b>	-	-	-
1	Pramipexole (Mirapex)	0.125–1	1.50-3.0	nausea, fatigue, somnolence, headache, augmentation
2	Ropinirole	0.25	0.5–4.0	impulse control disorders insomnia, dyspepsia, dizziness and 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	15-20	dyspepsia, nausea, headache, rhinitis and cardiac dysfunction
8	Codeine	2.50-15	50-100	nausea, sedation and respiratory depression
9	Hydrocodone or Methadone	1 -2.5	5.0-40	constipation, nausea, dizziness, sedation and potential for drug addiction / tolerance



## 12. CONCLUSION AND FUTURE DIRECTIONS

There is no known cure for RLS or no single drug works for everybody. We have some idea about the cause of RLS, but we have miles and miles left to overcome before we reach a level of understanding of RLS and miles more again before we predict or prevent its occurrence. Physicians suggest certain lifestyle changes and activities to reduce adverse symptoms. Patients with moderate to severe RLS typically require daily medication to control their symptoms. Although the dopamine agonists, ropinirole and pramipexole have been the drugs of choice for patients with moderate to severe RLS, drug emergent problems like augmentation may limit their use for long term therapy. Keeping the dopamine agonist dose as low as possible, using longer acting dopamine agonists such as the rotigotine patch and maintaining a high serum ferritin level may help prevent the development of augmentation. The  $\alpha 2\delta$  anti-convulsants may now also be considered as drugs of choice for moderate to severe RLS patients. Opioids should be considered for RLS patients, especially for those who have failed other therapies since they are very effective for severe cases.

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. This will encourage scientists/clinicians to develop more safe and effective drugs for this 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.

### CONSENT

Not applicable.

### ETHICAL APPROVAL

Not applicable.

The author is thankful to Prof. Jaishree Ghanekar, Head, Department of Internal Medicine and all the faculty of the Internal Medicine Department, MGM Medical College and Hospital, Navi Mumbai, India for their encouragements and support.

### COMPETING INTERESTS

Author has declared that no competing interests exist.

### REFERENCES

1. Ekblom KA. Asthenia CrurumParaesthica (irritable legs). *Acta Med Scand.* 1944;118:197-209.
2. Konofal E, Karroum E, Montplaisir J, Derenne JP, Arnulf I. Two early descriptions of restless syndrome and periodic legs movements by Boissier de Sauvages (1763) and Gilles de la Tourette (1898). *Sleep Med.* 2009;10:586-91.
3. Konofal E, Cortese S, Marchand M, Mouren MC, Arnulf I, Lecendreux M. Impact of restless legs syndrome and iron deficiency on attention-deficit/hyperactivity disorder in children. *Sleep Med.* 2007;8:711-15.
4. Walters AS, Hening W, Rubinstein M and Chokroverty S. A clinical and polysomnographic comparison of neuroleptic-induced akathisia and the idiopathic restless legs syndrome. *Sleep.* 1991;14:339-45.
5. Ekblom KA. Restless legs: A clinical study. *Acta Med Scand.* 1945;158:1-123.
6. Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Dopamine agonists for restless legs syndrome. *Cochrane Database Syst Rev.* 2011;16: CD006009.
7. Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA and Rye DB. An algorithm for the management of Restless Legs Syndrome. *Mayo ClinProc.* 2004;79:916-22.
8. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med.* 2005;165:1286-92.
9. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: Diagnostic

- criteria, special considerations, and epidemiology. *Sleep Med.* 2003;4:101-19.
10. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A and Ferini-Strambi L. Impact, diagnosis and treatment of Restless Legs Syndrome in a primary care population: REST (RLS epidemiology, symptoms and treatment) primary care study. *Sleep Med.* 2004;5:237-46.
  11. Moore Y. *Sleep: A comprehensive handbook.* Chapter 4: Biological rhythms and sleep. John Wiley and sons. Inc. 2006;25-9.
  12. Becker PM, Novak M. Diagnosis, comorbidities, and management of restless legs syndrome. *Current Medical Research & Opinion.* 2014;30:1441-60.
  13. Lavigne G, Montplaisir J. Restless legs syndrome and sleep bruxism: Prevalence and association among Canadians. *Sleep.* 1994;17:739-43
  14. Trenkwalder C, Seidel VC, Gasser T, Oertel WH. Clinical symptoms and possible anticipation in large kindred of familial restless legs syndrome. *Movement Disorder.* 1996;11:389-94.
  15. Zucconi M, Ferini-Strambi L. Epidemiology and clinical findings of restless legs syndrome. *Sleep Med.* 2004;5:293-99.
  16. Tan E, Koh K, See S. Restless legs syndrome in an Asian population: A study in Singapore. *Mov Disord.* 2001;16:577-59.
  17. Ulfberg J, Bjorvatn B, Leissner L, Gyring J, Karlsborg M, Regeur L, Skeidsvoll H, Polo O, Partinen M. Comorbidity in restless legs syndrome among a sample of Swedish adults. *Sleep Med.* 2007;7:768-72.
  18. Wesström J, Nilsson S, Sundström-Poromaa I, Ulfberg J. Restless legs syndrome among women: Prevalence, comorbidity and possible relationship to menopause. *Climacteric.* 2008;11:422-28.
  19. Dzaja A, Wehrle R, Lancel M, Pollmacher T. Elevated estradiol plasma levels in women with restless legs during pregnancy. *Sleep.* 2009;32:169-74.
  20. Cortese S, Konofal E, Lecendreux M, et al. RLS and attention-deficit/hyperactivity disorder: A review of the literature. *Sleep.* 2005;28:722-28.
  21. Rajaram SS, Walters AS, England SJ, Mehta D, Nizam F. Some children with growing pains may actually have RLS. *Sleep.* 2004;27:767-73.
  22. Pullen SJ, Wall CA, Angstman ER, Munitz GE and Kotagal S. Psychiatric comorbidity in children and adolescents with restless legs syndrome: A retrospective study. *J Clin Sleep Med.* 2011;7:587-96.
  23. Basu A, Kundu S, Khuran H. Olanzapine-induced restless legs syndrome: A case report and review of literature. *Indian Journal of Pharmacology.* 2014;46:450-452.
  24. Mizuno S, Mihara T, Miyaoka T, Inagaki T, Horiguchi J. CSF iron, ferritin and transferrin levels in restless legs syndrome. *J Sleep Res.* 2005;14:43-7.
  25. Zhang C, Li Y, Malhotra A, Ning Y, Gao X. Restless legs syndrome status as a predictor for lower physical function. 2014;82:1212-1218.
  26. Wang J, O'Reilly B, Venkataraman R, Mysliwiec V, Mysliwiec A. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study. *Sleep Med.* 2009;10:973-75.
  27. Sun ER, Chen CA, Ho G, Earley CJ and Allen RP. Iron and the restless legs syndrome. *Sleep.* 1998;21:371-77.
  28. Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. *Sleep Med.* 2000;1:11-9.
  29. Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology.* 2000;54:1698-70.
  30. Cooper JB, Roth R. *The biochemical basis of neuropharmacology.* Oxford University Press, New York; 1991.
  31. Taylor-Gjevre RM, Gjevre JA, Skomro R, Nair B. Restless legs syndrome in a rheumatoid arthritis patient cohort. *J Clin Rheumatol.* 2009;15:12-19.
  32. Hui DS, Wong TY, Ko FW. Prevalence of sleep disturbances in Chinese patients with end-stage renal failure on continuous ambulatory peritoneal dialysis. *Am J Kidney Dis.* 2000;36:783-88.
  33. Banerji N and Hurwitz L. Restless legs syndrome, with particular reference to its occurrence after gastric surgery. *Br Med J.* 1970;4:774-75.
  34. Zobeiri M, Shokoohi A. Restless legs syndrome in diabetics compared with normal controls. *Sleep Disorders;* 2014. Article ID: 871751.
  35. Silber MH, Richardson JW. Multiple blood donations associated with iron deficiency in patients with restless legs syndrome. *Mayo Clin Proc.* 2003;78:52-54.

36. Winkelmann J, Muller-Myhsok B, Wittchen HU, Hock B, Prager M, Pfister H, Strohle A, Eisensehr I, Dichgans M, Gasser T and Trenkwalder C. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. *Ann Neurol.* 2002;52:297–302.
37. Bonati MT, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M, Casari G. Autosomal dominant restless legs syndrome maps on chromosome 14q. *Brain.* 2003;126:1485-92.
38. Desautels A, Turecki G, Rouleau GA. Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q. *Am J Hum Genet.* 2001;69:1266-70.
39. Winkelmann J, Wetter TC, Collado-Seidel V, Gasser T, Dichgans M, Yassouridis A, Trenkwalder C. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. *Sleep.* 2000;23:597-602.
40. Hornyak M, Feige B, Riemann D, Voderholzer U. Periodic limb movements in sleep and periodic limb movement disorder: Prevalence, clinical significance and treatment. *Sleep Med Rev.* 2006;10:169-77.
41. Symonds CP. Nocturnal myoclonus. *J Neurol Neurosurg Psychiatry.* 1953;16:166-71
42. Zucconi M, Manconi M. Sleep disturbances in restless legs syndrome (RLS) and periodic limb movements (PLM). Editors: Pandi-Perumal SR, Monti JM. In: *Clinical Pharmacology of Sleep.* Basel: Birkhäuser Verlag. 2006;61–79.
43. Neikrug AB, Ancoli-Israel S. Sleep disorders in the older adult. A mini review. *Gerontology.* 2010;56:181–89.
44. Meena G, Batra A, Trivedi A, Chowdhury D, Khwaja G. Restless legs syndrome, periodic limb movements, febrile seizures and Attention deficit hyperactivity disorder in an Indian family. *Ann Indian Acad Neurol.* 2012;15:39-43.
45. Rangarajan S, Rangarajan S, D'Souza GA. Restless legs syndrome in Indian patients having iron deficiency anemia in a tertiary care hospital. *Sleep Med.* 2007;8:247–55.
46. Bhowmik D, Bhatia M, Gupta S, Agarwal SK, Tiwari SC, Dash SC. Restless legs syndrome in hemodialysis patients in India: A case controlled study. *Sleep Med.* 2003;4:143–46.
47. Lee KA, Zaffke ME, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. *J Womens Health Gen Based Med.* 2001;10:335-41.
48. Manconi M, Ferini-Strambi L. Restless legs syndrome among pregnant women. *Sleep.* 2004;27:250.
49. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. *Arch Internal Med.* 2004;164:196–202.
50. Murphy PJ, Campbell SS. Sex hormones, sleep, and core body temperature in older postmenopausal women. *Sleep.* 2007;12:1788-94.
51. Picchiatti DL, Wang VC, Picchiatti MA. Intravenous iron given prior to pregnancy for restless legs syndrome is associated with remission of symptoms. *J Clin Sleep Med.* 2012;15:585-86.
52. Malek A. *In vitro* studies of ferric carboxymaltose on placental permeability using the dual perfusion model of human placenta. *Arzneimittelforschung.* 2010;60:354-56.
53. Chen S, Ondo WG, Rao S, Li LQ, Wang Q. Genomewide linkage scan identifies a novel susceptibility locus for restless legs syndrome on chromosome 9p. *Am J Hum Genet.* 2004;74:876-85.
54. Lohmann-Hedrich K, Neumann A, Kleinsang A, Lohnau T, Muhle H, Djarmati A, König IR, Pramstaller PP, Schwinger E, Kramer PL, Ziegler A, Stephani U and Klein C. Evidence for linkage of restless legs syndrome to chromosome 9p: are there two distinct loci? *Neurology.* 2008;70:686-94.
55. Yeh P, Walters AS, Tsuang JW. Restless legs syndrome: A comprehensive overview on its epidemiology, risk factors, and treatment. *Sleep Breath.* 2012;16:987-1007.
56. Ondo WG, Vuong KD, Wang Q. Restless legs syndrome in monozygotic twins: clinical correlates. *Neurology.* 2000;55:1404-09.
57. Pichler I, Marroni F, Volpato CB, Pramstaller PP. Linkage analysis identifies a novel locus for restless legs syndrome on chromosome 2q in a South Tyrolean population isolate. *Am J Hum Genet.* 2006;79:716-23.
58. Levchenko A, Montplaisir JY, Asselin G, Provost S, Girard SL, Xiong L, Lemyre E,

- St-Onge J, Thibodeau P, Desautels A, Turecki G, Gaspar C, Dubé MP, Rouleau GA. Autosomal dominant locus for restless legs syndrome in French-Canadians on chromosome 16p12.1. *Movement Disorder*. 2009;24:40–50.
59. Xiong L, Catoire H, Dion P, Gaspar C, Lafrenière RG, Girard SL, Levchenko A, Rivière JB, Fiori L, St-Onge J, Bachand I. MEIS1 intronic risk haplotype associated with restless legs syndrome affects its mRNA protein expression levels. *Hum Mol Genet*. 2009;18:1065-74.
  60. Winkelmann J, Schormair B, Lichtner P, Ripke S, Xiong L, Jalilzadeh S, Fulda S, Pütz B, Eckstein G, Hauk S, Trenkwalder C. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. *Nat Genet*. 2007;39:1000-6.
  61. Spieler D, Kaffe M, Knauf F, Bessa J, Tena JJ, Giesert F, Schormair B, Tilch E, Lee H, Horsch M, Czamara D, et al. Restless Legs Syndrome-associated intronic common variant in Meis1 alters enhancer function in the developing telencephalon. *Genome Research*. 2014;24:592-603.
  62. Yang Q, Li L, Yang R, Yang Q, Li L, Yang R, Shen GQ, Chen Q, Schaefer FN, Ondo WG, Wang QK. Family-based and population-based association studies validate PTPRD as a risk factor for restless legs syndrome. *Mov Disord*. 2011;26:516-19.
  63. Pichler I, Hicks AA, Pramstaller PP. Restless legs syndrome: An update on genetics and future perspectives. *Clin Genet*. 2008;73:297–305.
  64. Winkelmann J, Lichtner P, Schormair B, Uhr M, Hauk S, Stiasny-Kolster K, Trenkwalder C, Paulus W, Peglau I, Eisensehr I, et al. Variants in the neuronal nitric oxide synthase (nNOS, NOS1) gene are associated with restless legs syndrome. *Movement Disorder*. 2008;23:350–358.
  65. Kushida C, Martin M, Nikam P, Blaisdell B, Wallenstein G, Ferini-Strambi L, Ware JE Jr, et al. Burden of restless legs syndrome on health-related quality of life. *Qual Life Res*. 2007;16:617-24.
  66. McDonagh B, King T, Guptan RC. Restless legs syndrome in patients with chronic venous disorders: An untold story. *Phlebology*. 2007;22:156–63.
  67. Manconi M, Ulfberg J, Berger K, Ghorayeb I, Westrom J, Fulda S, Allen RP, Pollmächer T. When gender matters: restless legs syndrome. Report of the "RLS and woman" workshop endorsed by the European RLS Study Group. *Sleep Med Rev*. 2012;16:297-307.
  68. Lin CH, Wu VC, Li WY, Sy HN, Wu SL, Chang CC, Chiu PF, Lion HH, Lin CY, Chang HW, Lin SY, Wu KD, Chen YM, Wu RM. Restless legs syndrome in end-stage renal disease: A multicenter study in Taiwan. *Eur J Neurol*. 2013;20:1025- 31.
  69. Gao X, Schwarzschild MA, O'Reilly EJ, Wang H, Ascherio A. Restless legs syndrome and erectile dysfunction. *Sleep*. 2010;33:75-79.
  70. Stehlik R, Arvidsson L, Ulfberg J. Restless legs syndrome is common among female patients with fibromyalgia. *Eur Neurol*. 2009;61:107-11.
  71. Merlino G, Fratticci L, Valente M, Del Giudice A, Noacco C, Dolso P, Cancelli I, Scalise A, Gigli GL. Association of restless legs syndrome with type 2 diabetes: A case-control study. *Sleep*. 2007;30:866-71.
  72. Hattan E, Chalk C, Postuma RB. Is there a higher risk of restless legs syndrome in peripheral neuropathy? *Neurology*. 2009;72:955-60.
  73. Innes KE, Selfe TK, Agarwal P. Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: A systematic review. *Sleep Med Rev*. 2012;16:309-39.
  74. Winter AC, Schürks M, Glynn RJ, Buring JE, Gaziano JM, Berger K, Kurth T. Restless legs syndrome and risk of incident cardiovascular disease in women and men: Prospective cohort study. *Br Med J*. 2012;2:1-9.
  75. Chen PK, Fuh JL, Chen SP, Wang SJ. Association between restless legs syndrome and migraine. *J Neurol Neurosurg Psychiatry*. 2010;81:524-30.
  76. Morselli L, Leproult R, Balbo M and Spiegel K. Role of sleep duration in the regulation of glucose metabolism and appetite. *Best Pract Res Clin Endocrinol Metab*. 2010;24:687-702.
  77. Ferini-Strambi L, Walters AS, Sica D. The relationship among restless legs syndrome (Willis-Ekbom Disease), hypertension, cardiovascular disease, and cerebrovascular disease. *J Neurol*. 2014;261:1051-68.
  78. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and

- periodic limb movements in sleep to hypertension, heart disease, and stroke. *Sleep*. 2009;32:589-97.
79. Benediktsdottir B, Janson C, Lindberg E, Arnardottir ES, Olafsson I, Cook E, et al. Prevalence of restless legs syndrome among adults in Iceland and Sweden: Lung function, comorbidity, ferritin, biomarkers and quality of life. *Sleep Med*. 2012;11:1043-48.
  80. Peeraully T, Tan EK. Linking restless legs syndrome with Parkinson's disease: Clinical, imaging and genetic evidence. *Translational Neurodegeneration*. 2012;1:6-12.
  81. Gudbjörnsson B, Broman JE, Hetta J, Hällgren R. Sleep disturbances in patients with primary Sjögren's syndrome. *Br J Rheumatol*. 1993;32:1072-76
  82. Hassan N, Pineau CA, Clarke AE, Vinet E, Ryan NG, Bernatsky S. Systemic lupus and risk of restless legs syndrome. *J Rheumatol*. 2011;38:874-879.
  83. Salih AM, Gray RE, Mills KR, Webley M. A clinical, serological and neurophysiological study of restless legs syndrome in rheumatoid arthritis. *Br J Rheumatol*. 1994;33:60-63.
  84. Li Y, Munger KL, Batool-Anwar S, De Vito K, Ascherio A, Gao X. Association of multiple sclerosis with restless legs syndrome and other sleep disorders in women. *Neurology*. 2012;78:1500-06.
  85. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry*. 2003;60:39-47.
  86. Szentkirályi A, Völzke H, Hoffmann W, Happe S, Berger K. A time sequence analysis of the relationship between cardiovascular risk factors, vascular diseases and restless legs syndrome in the general population. *J Sleep Res*. 2013;22:434-42.
  87. Richey F, Makaroff L, Pietri G, et al. Restless Legs Syndrome (RLS) and Subsequent Cardiovascular (CV) risk in a US observational setting. Presented at the 63rd Annual Meeting of the American Academy of Neurology, Hawaii, USA; 2011.
  88. Ulfberg J, Nystrom B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov Disord*. 2001;16:1159-63.
  89. Ferri R, Fulda S, Manconi M, Hogl B, Ehrmann L, Ferini-Strambi L, Zucconi M. Night-to-night variability of periodic legs movements during sleep in restless legs syndrome and periodic limb movement disorder: Comparison between the periodicity index and the PLMS index. *Sleep Med*. 2013;14:293-96.
  90. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: Results from the health professional's follow-up study. *Ann Internal Med*. 2003;139:161-68.
  91. Gao X, Chen H, Ascherio A. Erectile function and risk of Parkinson's disease. *Am J Epidemiol*. 2007;166:1446-450.
  92. Maheswaran M, Kushida CA. Restless legs syndrome in children. *Medscape Gen Med*. 2006;8:79.
  93. Ghosh A, Basu D. Restless legs syndrome in opioid dependent patients *Indian J of Psychological Med*. 2014;36:85-87.
  94. Allen RP, Barker PB, Horska A, Earley CJ. Thalamic glutamate/glutamine in restless legs syndrome: Increased and related to disturbed sleep. *Neurology*. 2013;80:2028-34.
  95. Ondo WG, Vuong KD, Jankovic J. Exploring the relationship between Parkinson disease and restless legs syndrome. *Arch Neurol*. 2002;59:421-24.
  96. Buchfuhrer MJ. Strategies for the treatment of restless legs syndrome. *Neurotherapeutics*. 2012;9:776-90.
  97. Ferini-Strambi L, Aarskog D, Partinen M, et al. Effect of pramipexole on RLS symptoms and sleep: A randomized, double-blind, placebo-controlled trial. *Sleep Med*. 2008;9:874-881.
  98. Cuellar N, Galper D, Taylor A, D'Huyvetter K, Miederhoff P, Stubbs P. Restless legs syndrome. *J Altern Complement Med*. 2004;10:422-423.
  99. Cui Y, Wang Y, Liu Z. Acupuncture for restless legs syndrome (review) *Cochrane Database Syst Rev*. 2008;4:CD006457.
  100. Rajaram S, Shanahan J, Ash C, Walters A, Weisfogel G. Enhanced external counter pulsation (EECP) as a novel treatment for Restless Legs Syndrome (RLS): A preliminary test of the vascular neurologic hypothesis for RLS. *Sleep Med*. 2005;6:101-106.
  101. Burbank F, Buchfuhrer MJ, Kopjar B. Improving sleep for patients with restless legs syndrome. Part II: Meta-analysis of

- vibration therapy and drugs approved by the FDA for treatment of restless legs syndrome. *J Parkinsonism Restless Legs Syndrome*. 2013;3:11-22.
102. Phillips B, Young T, Finn L, Asher K, Hening W, Purvis C. Epidemiology of restless legs symptoms in adults. *Arch Internal Med*. 2000;160:2137-41.
  103. Clifford P, Hellsten Y. Vasodilatory mechanisms in contracting skeletal muscle. *J Appl Physiol*. 2004;97:393-403.
  104. Akpinar S. Restless legs syndrome treatment with dopaminergic drugs. *Clin Neuropharmacol*. 1987;10:69-79.
  105. Earley CJ, Allen RP. Pergolide and carbidopa/levodopa treatment of the restless legs syndrome and periodic legs movements in sleep in a consecutive series of patients. *Sleep*. 1996;19:801-10.
  106. Winkelmann J, Schadrack J, Wetter TC, Zieglgansberger W, Trenkwalder C. Opioid and dopamine antagonist drug challenges in untreated restless legs syndrome patients. *Sleep Med*. 2001;2:57-61.
  107. Allen RP, Chen C, Garcia-Borreguero D, Polo O, DuBrava S, Miceli J, Knapp L and Winkelman JW. Comparison of pregabalin with pramipexole for restless legs syndrome. *New England J Med*. 2014;370:621-31.
  108. Horvath J, Fross RD, Kleiner-Fisman G, Lerch R, Stalder H, Liaudat S, Raskoff WJ, Flachsbarth KD, Rakowski H, Pache JC, Burkhard PR, Lang AE. Severe multivalvular heart disease: A new complication of the ergot derivative dopamine agonists. *Mov Disord*. 2004;19:656-62.
  109. Trenkwalder C, Benes H, Poewe W, Oertel WH, Garcia-Borreguero D, de Weerd AW, Ferini-Strambi L, Montagna P, Odin P, Stiasny-Kolster K, Högl B, et al. Efficacy of rotigotine for treatment of moderate-to-severe RLS: A randomized, double-blinded, placebo-controlled trial. *Lancet Neurol*. 2008;7:595-604.
  110. Hayes WJ, Lemon MD, Farver DK. Gabapentin enacarbil for treatment of restless legs syndrome in adults. *Ann Pharmacother*. 2012;46:229-39.

© 2015 Reddy; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*

*The peer review history for this paper can be accessed here:*  
<http://www.sciencedomain.org/review-history.php?iid=719&id=12&aid=6964>