

# Restless Legs Syndrome: Pathophysiology and Treatment

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## Opinion statement

Restless legs syndrome (RLS) is a complicated sensory-motor syndrome. The pathology is increasingly understood, but a clear physiologic understanding still remains elusive. The most robust findings remain reduced central nervous system (CNS) iron and some perturbation in dopaminergic systems. Other neurotransmitter systems are also likely involved, and the phenotype may result from distinct pathophysiologic processes. Treatment of RLS is often very successful, and treatment goals should be high. Dopamine agonists may most robustly improve pure urge to move and certainly periodic limb movements. They do not directly improve sleep, and long-term use is limited by augmentation. Alpha-2-delta ligand drugs such as gabapentin enacarbil and pregabalin improve RLS, presumably in a less specific manner. These drugs increase slow wave sleep and improve pain, but have less impact on leg movements. Mu specific opioids also robustly improve RLS and are probably underutilized in severe cases. Intravenous iron inconsistently but sometimes considerably improves RLS and can be considered in refractory cases.

## Introduction: clinical RLS

Restless legs syndrome (RLS) is clinically defined by the presence of four criteria: 1) an urge to move the limbs with or without uncomfortable sensations, 2) worsening at rest, 3) improvement with activity, 4) worsening in the evening or at night [1•]. Additional criteria now stipulate that these symptoms not be caused by another etiology. The diagnosis of RLS is exclusively based on those symptoms. The patient subjective descriptions, however, are

quite varied and tend to be suggestible and education dependent. The sensation is always unpleasant, but not necessarily “painful.” It is usually deep within the legs and commonly between the knee and ankle. Patients usually deny any “burning” or “pins and needles” sensations, commonly experienced in neuropathies or nerve entrapments, although neuropathic pain and RLS can co-exist. Most patients report transient symptomatic

improvement by walking, although other movements also help. Other therapeutic techniques reported by patients include rubbing or pressure, stretching, and hot water. In general, harsh sensory stimuli can mitigate RLS. Cognitive or emotional activating circumstances (i.e., arguing) also often reduce RLS. Other clinical features typical for RLS include the tendency for symptoms to gradually worsen with age, improvement with dopaminergic treatments, a positive family history, and periodic limb movements while asleep (PLMS).

PLMS are defined by the American Academy of Sleep Medicine as “periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep.” They classically occur every 20–40 seconds, mostly in Stage I and II sleep. PLMS are common in the general population, and incidence increases with age. However, they are seen in more than 80 % of RLS patients [2]. Therefore, most people with RLS have PLMS, but many patients with isolated PLMS do not have RLS. PLMS are associated with an autonomic spike just before the movement, with transient increase in both blood pressure and pulse. This is increasingly scrutinized, as it is postulated to account for the correlation between PLMS and RLS, and risk of cardiovascular disease seen in some [3–6], but not all studies [7, 8]. Dopaminergics used to

treat PLMS also blunt the autonomic response, as well as the actual movement [9]. In contrast, K-complexes and arousals that usually precede the PLMS may persist even if PLMS are reduced [10].

Although some children report classic RLS symptoms that meet inclusion criteria, other complain of “growing pains” [11, 12], and some appear to present with an attention deficit hyperactivity disorder (ADHD) phenotype. Diagnostic criteria for RLS in children is less well validated, but emphasizes supportive criteria such as a family history of RLS, sleep disturbances, the presence of PLMS, and typical descriptors used by children [13].

RLS is very common. Studies in predominantly Caucasian populations consistently show that between 5 and 15 % of people have RLS, which is clinically significant in 2–3 % [14]. In general, northern European countries demonstrate the highest prevalence, followed by Germanic/Anglo-Saxon, and then Mediterranean countries. The prevalence tends to decline the farther east one progresses, dropping to less than 1 % in Singapore. People from African have never been specifically studied, but anecdotally, African Americans only rarely present with RLS. Women usually have higher RLS rates. However, this female preponderance is lost in null-parous women [15, 16].

## Pathophysiology of RLS

Pathophysiological studies show a number of abnormalities in patients with RLS; however, our understanding is far from complete. Abnormalities in circadian physiology, iron, dopamine, glutamate, and opioid systems within the central nervous system (CNS) have been identified. Peripheral nervous systems show abnormalities in sensory perception. Several genetic alleles increase the risk of RLS, which has a strong genetic component. A number of other conditions in which RLS is more commonly seen also provide pathophysiological clues.

### Iron

The most robust and consistent observation is reduced CNS iron stores, even in the setting of normal systemic iron studies. CSF ferritin is lower in RLS cases [17], and specially sequenced magnetic resonance imaging (MRI) studies show reduced iron stores in the striatum and red nucleus [18, 19]. CNS ultrasonography is also able to identify RLS based on reduced iron echogenicity in the substantia nigra (SN) [20, 21]. Most importantly, pathologic data in RLS autopsied brains show reduced H-ferritin staining, iron staining, and increased transferrin stains, but also reduced transferrin receptors [22]. Mitochondrial ferritin, however, is increased in neurons in the SN but not putamen of RLS subjects [23].

The reduced transferrin receptor finding is especially important, because globally reduced iron stores would normally upregulate transferrin receptors. Therefore, it appears that primary RLS has reduced intracellular iron indices associated with a perturbation of homeostatic mechanisms that regulate iron influx or efflux from the cell. Intracellular iron regulation is very complex; however, subsequent staining of RLS brains has shown reduced levels of iron regulatory protein-type 1 (IRP-1) [22]. This potentiates or inhibits (depending on feedback mechanisms involving iron atoms themselves) the production of ferritin molecules, which are the main iron storage proteins in the CNS as well as the periphery, and transferrin receptors, which facilitate intracellular iron transport. Whether reduced iron manifests the symptoms of RLS, or is just an epiphenomenon, is not known.

## Dopamine

CNS dopaminergic systems are most implicated in RLS by the vigorous symptom improvement seen with dopaminergics. The normal circadian dopaminergic variation is also augmented in patients with RLS [24, 25]. However, there is little evidence to suggest any dopaminergic deficiency in patients with RLS. Pathologic studies have not found loss of dopamine cells or dopamine in the striatum or SN [26, 27]. Evidence of neurodegeneration markers, including Lewy bodies, plaques or tangles, is also absent [28]. Dopamine marker pathologic studies have been difficult to interpret. SN tyrosine hydroxylase, the rate-limiting step in dopamine synthesis, both phosphorylated (active) and non-phosphorylated (inactive), is increased in RLS subjects compared to controls [29]. There was some decrease in Dopamine-2 receptors in the putamen, but no change in dopamine-1 receptors. Vesicular monoamine transporter (VMAT), a marker of dopamine storage, and other monoamine markers were normal.

Brain imaging studies are inconsistent and show modest or no abnormalities [30–33]. Briefly, dopamine precursor studies show normal or reduced levels, dopamine transporter studies have been normal or reduced, and dopamine receptor studies show reduced, normal, or increased activity. Two studies using different ligands from the same group are interpreted as showing increased dopamine turnover [34]. It should be noted that functional brain imaging studies mostly reflect activity in the striatum, the largest dopaminergic area. Other smaller dopaminergic areas, which may be involved in RLS, are too small to image.

Other indirect evidence suggests increased dopamine turnover in RLS. Cerebrospinal fluid (CSF) 3-Ortho-methyldopa (OMD) is increased in RLS subjects, suggesting either increased dopamine metabolism in general, or specifically increased monoamine oxidase (MAO)-B activity, which metabolizes dopamine to 3-OMD [35]. These data have led some to speculate that RLS is a disease of hyperdopaminergic function. However, this does not explain the dramatic and immediate benefit of dopaminergics.

The identification of a specific anatomical site in RLS remains another puzzle. The spinal cord and sub-cortex are implicated in studies of RLS onset after stroke and spinal cord injuries [36]. More specifically, involvement of the little-studied diencephalospinal dopaminergic tract, originating from the A11-A14 nuclei, might explain some RLS features. It is involved in anti-nociception, is near circadian control centers, and would explain why legs are involved more than arms. A preliminary animal model with A11 lesions demonstrated

increased standing episodes, which improved after the administration of ropinirole, a dopamine agonist [37]. Subsequent studies of this model in mice, with and without dietary iron deprivation, also demonstrate increased movement, as measured in laser marked cages, in the lesioned animals [38]. This hyperkinesia is normalized by D2 agonists such as ropinirole and pramipexole, but not by the D1 agonist SKF, which actually increased movement further. This small area is not visible with dopamine imaging and would probably not contribute meaningfully to CSF dopamine studies. No careful study examining spinal cord dopamine metabolites/receptors exists. Human pathologic studies of the dopaminergic neurons of the A11 system, however, have not shown any cell loss [39].

There are several potential interactions between iron and dopamine systems. First, iron is a co-factor for tyrosine-hydroxylase (TH), which is the rate-limiting step in the production of dopamine. However, TH activity is actually increased in humans with RLS, so this is unlikely. Second, iron is a component of the dopamine type-2 (D2) receptor. Iron deprivation in rats results in a 40–60 % reduction of D2 post-synaptic striatal, but not spinal cord receptors [40, 41]. The effect in the striatum is quite specific, as other neurotransmitter systems, including D1 receptors, are not affected. However, the dramatic and immediate response to dopamine agonists would be difficult to explain in the setting of receptor deficiency. Third, iron is necessary for Thy1 protein regulation. This cell adhesion molecule, which is robustly expressed on dopaminergic neurons, is reduced in brain homogenates in iron-deprived mice [42] and in brains of patients with RLS [43]. Thy1 regulates vesicular release of monoamines, including dopamine [44]. It also stabilizes synapses and suppresses dendritic growth [45]. Further work on this possible connection is warranted.

## Opioid systems

Opioid pathways are implicated by clinical improvement seen with narcotics and pathological data that show reduced Beta-endorphin positive cells (37.5 %,  $p=0.006$ , effect size 2.16) and Met-enkephalin positive cells (26.4 %,  $p=0.028$ , effect size 1.58) in six RLS patients compared to six controls [26]. Dopamine activity was normal in this study. Positron emission tomography (PET) imaging studies using non-specific opioid ligands did not differentiate between human RLS and controls, but did correlate with severity within the RLS group, suggesting that the more severe the RLS, the greater the release of endogenous opioids within the medial pain system [46].

Afferent systems are also implicated [47, 48]. Stiasny-Kolster reported that pin-prick pain ratings (static hyperalgesia) in RLS patients were significantly elevated in the lower limb, whereas pain to light touch (allodynia = dynamic mechanical hyperalgesia) was normal. They felt this type of hyperalgesia was probably mediated by central sensitization to A-delta fiber high-threshold mechanoreceptor input, a hallmark sign of the hyperalgesia type of neuropathic pain.

## Miscellaneous studies

Recently, (1)H magnetic resonance spectroscopy (MRS) showed increased glutaminergic activity in the thalamus of RLS patients [49]. This correlated with

increased arousal, but not PLMS. This study, however, was contradicted by a later report by Winkelman et al., who found increased gamma-aminobutyric acid (GABA) in the thalamus using MR spectroscopy [50].

A single cerebrospinal fluid (CSF) proteomics trial of only five subjects found four proteins that were increased in RLS (Cystatin C, Lipocalin-type Prostaglandin D2 Synthase, Vitamin D binding Protein, and beta-Hemoglobin) and two proteins (Apolipoprotein A1 and alpha-1-acid Glycoprotein) that were decreased [51].

Functional MRI studies show increased activity in the cerebellum and thalamus during the sensory component, which also included the red nucleus and brainstem reticular formation during the sensory/motor component [52]. MRI voxel-based morphometry has shown several inconsistent abnormalities, of which increased pulvinar grey matter seems the most robust [53].

## RLS genetics

In 40–60 % of cases, a family history of RLS can be found, although this is often not initially reported by the patient [54]. Twin studies also show a very high concordance rate [55, 56]. Most pedigrees suggest an autosomal dominant (AD) pattern [57], although an autosomal recessive (AR) pattern with a very high carrier rate is possible. Many linkages have been identified in traditional familial studies, but in no case has a specific gene mutation been identified [Table 1]. A number of candidate genes, including those involved with dopamine metabolism, Parkinson's disease, neurodegeneration, and systemic iron regulation, have generally been unrevealing [74]. To date, six risk factor genes, identified through genome-wide association studies, have been published [Table 2]. Identification of the physiology of these genes is ongoing. Several of these are thought to be developmental genes and at least one is now associated with iron regulation. Recently, these genes did not show any association in Asian uremic RLS patients [75]. As with other common conditions, the genetics of RLS are complex and probably involve the presence of multiple at risk genetic alleles.

## Pathophysiologic clues from associated conditions

The most common diseases associated with RLS include renal failure, iron deficiency, neuropathy, myelopathy, pregnancy, multiple sclerosis, and possibly Parkinson's disease and essential tremor. Many other additional reported associations are less well established. The exact relationship between these conditions and RLS is not known, but several patterns of interest exist.

Neuropathy and myelopathy both result in deafferentation. This is intuitive, since sensory stimulation (pain, heat, etc.) improves RLS. Alteration in iron homeostasis is seen in systemic iron deficiency, uremia, and pregnancy. Systemic iron deficiency correlates with RLS, mostly in those with an older age of onset and in those who lack a family history of RLS, suggesting it is a true secondary cause, resulting in similar symptoms to those with a presumed genetic cause of RLS. Data on whether iron deficiency specifically correlates with RLS in uremia are sparse. Uremia is a complex biochemical condition and most subjects on dialysis receive aggressive iron supplementation. RLS seems to improve with successful kidney transplantation, but not with dialysis [76–79].

**Table 1. Genes and linkages associated with RLS**

Chrom	Gene	Method	Odds ratio	Comment
6p21.2	BTBDP	GWAS	1.3 (1.04–1.7)	Zinc Finger [58, 59]
2p	MEIS1	GWAS	1.7 (1.4–2.1)	homobox gene [59]
15q	MAP2K5/ LBOXCOR1	GWAS	1.5 (1.2–1.9)	mitogen-activated protein kinase [59]
9p23-24	PTPRD	GWAS	1.4	protein tyrosine phosphatase receptor type delta [60]
16q12.1	TOX3	GWAS	1.33	
2p14	Intergenic	GWAS	1.23	
	MAO-A	candidate	2.0 (1.1–3.8)*	High activity allele in women only* [61]
	NOS1	candidate	0.76 (0.6–0.9)	neuronal nitric oxide synthase-1 [62]
12q22-23		linkage		AR French Canadian Family[63]
14q13-21		linkage		AD Italian [64]
9p24.2-22.3		linkage		No mutation in PTPRD found, AD, USA [65]
2q33	K <sup>+</sup> channel-related gene KCTD18 and SPATS2L	linkage		South Tyrolean [66]
20p13		linkage		French Canadian, AD [67]
20p13		linkage		Dutch family (4.5 Mb)[68]
9p		linkage		May be different from US families, German [69]
16p12.1		linkage		AD, French Canadian [70]
19p13.3		linkage		AD Irish family (2.5 Mb area)[71]
13q32.3-33.2		linkage		Turkish family[72]
	PCDHA3	Exome Sequ		German family also WWC2, ATRN, and FAT2 genes[73]

GWAS = genome wide association studies  
Linkage = familial linkage studies  
Exome Sequ = exome wide sequencing

RLS in pregnancy correlates with low iron measures in some studies [80, 81]. Increased progesterone may also be culpable.

The relationship between Parkinson's disease (PD) and RLS has been extensively studied. Almost all studies of PD patients show increased prevalence of RLS, but in most cases, PD precedes RLS onset, although some studies suggest RLS occurs early in the course of PD [81, 82]. There is no evidence that early onset familial RLS is a risk factor for the subsequent development of PD, and in fact, some data suggest RLS may prevent PD [83]. The preponderance of data suggests that RLS in PD has a distinct pathophysiology from idiopathic RLS.

Several medications are also known to exacerbate existing RLS or possibly precipitate RLS themselves. The most notable of these include antihistamines, dopamine antagonists, including many anti-nausea medications, mirtazapine, possibly tricyclic antidepressants, and serotonergic reuptake inhibitors (SSRIs). Sedating antihistamines, which cross the blood brain barrier, most strongly exacerbate RLS. Many RLS patients have experienced this, especially since they are marketed as sleep aids. SSRIs are more associated with PLMS than RLS. Interestingly, dopamine antagonists do not usually worsen RLS and the dopamine release inhibitor tetrabenazine does not exacerbate RLS [84, 85].

**Table 2. Medications and doses used for RLS**

Drug	Dose (mg)	Duration of effect (hours)	Comment
Dopaminergics: immediate effect, considered first-line therapy			
L-dopa	100–250	2–6	Positive Class 1 trials, Approved in the EU, Fast onset, can use prn, highest augmentation rates
Pramipexole	0.125–1	5–12	Positive class 1 trials, Approved in the US and EU, Commonly used, slower onset but longer duration
Ropinirole	0.25–4	4–8	Approved US and EU, slow release preparations available
Rotigotine	1–3	24	Positive class 1 trials, Approved in the US and EU, Commonly used Patch preparation
Pergolide	0.125–1	6–14	Well studied (class 2), but seldom used due to risk of cardiac valve fibrosis and other possible ergot AEs
Apomorphine	1–3 mg	1	Injection of short acting powerful drug, anecdotal prn use
Cabergoline	0.25–2	> 24	Longest acting but may have same AEs as other ergot DAs
Bromocriptine	5–20	4–6	Rarely used in RLS
Opioids: numerous opioids are used			
Methadone	2–15	8–12	Open label data only, very good long term tolerability and efficacy, Several day latency to benefit
Hydrocodone	5–10	4–10	Faster acting, shorter duration
Oxycodone	10–40	4–10	Best studied opioid, with naloxone.
Alpha-2 delta blockers			
Gabapentin	300–1200	4–8	Small controlled trials, may help painful component of RLS
Pregabalin	50–300	6–12	Positive Class 1 and 2 trials, not approved
Gabapentin enacarbil	600–1200	8–16	Gabapentin prodrug with better absorption and pK profile. Positive class 1 trials, approved in the US
Benzodiazepines: more beneficial for sleep than RLS, can be used in combination with other RLS medications. Clonazepam (0.5–2.0 mg) is traditionally used.			
Oral iron	> 50	?	No specific iron salt superior, titrate up as tolerated. Ferritin will increase only modestly.
IV Iron preparations	1 gm	?	Usually not repeated before 3 months, several day latency to benefit, long-term safety unknown, Patients with “normal” serum ferritin equally responsive. Anecdotal evidence favors iron dextran preparations.

## Treatment of RLS

Multiple medications have demonstrated efficacy in well-designed clinical trials, and several treatment guidelines and evidence based reviews are published or in preparation [86, 87, 88, 89]. The best data support the use of dopaminergics, alpha2delta ligands, opioids, and iron. With the possible exception of iron, all are felt to provide only symptomatic relief, rather than any “curative” effect [Table 2]. Therefore, treatment should only be initiated when the benefits are felt to justify any potential side effects and costs. Treatment decisions also need to

consider the chronicity and general progressive course of RLS. Over time, both dosing and drug changes may be required to maximize benefit and minimize the risk of side effects. The quality of RLS symptoms and the timing of symptoms need to be considered to optimize treatment results.

## Dopaminergics

Dopamine agonists (DA) are the most investigated, consistently effective treatments for RLS. Most placebo-controlled trials usually show a 3–6 point improvement over placebo on the International RLS Rating Scale (IRLS). The large placebo response in RLS trials should be noted, and mitigate the importance of data that are not placebo controlled [90]. The improvement with DA is immediate and often very dramatic. No evidence favors any particular DA. Ropinirole [91–93], pramipexole [94–96], and rotigotine patches [97, 98] are the best studied and approved for use by European and American agencies. Pergolide [91, 99–102], bromocriptine [103], apomorphine [104], cabergoline [105] and lisuride [106] are also effective, but less commonly used. The dopamine precursor levodopa also effectively treats RLS and is officially licensed for use in some European countries [107, 108]; however, several comparative studies have favored DA over levodopa. [100, 109, 110]

Polysomnogram studies of DA consistently demonstrate dramatic improvement in PLMS, but only modest or no improvement in other sleep parameters. The effect is immediate, so titration to the smallest effective dose can be fairly rapid. Acute adverse events of DA in RLS studies are generally milder than in PD studies, perhaps owing to the lower dose or differences in the disease state. In contrast to PD, hallucinations and hypotension rarely occur in RLS, and daytime sedation may lessen rather than increase. Nausea remains the most common adverse event. Edema, impulse control disorders and nasal congestion still occur. The rotigotine 24-hour patch can cause an application site rash. Immediate release oral DA work best if administered at least 90 minutes before the onset of symptoms. Based on pharmacokinetics, many people may benefit from more than one dose, despite the formal indications, which recommend dosing 1–3 hours before bed. Extended release preparations of pramipexole and ropinirole are also very effective, but have not been formally studied in RLS.

Although the three approved DA have very similar receptor affinity profiles (all have a relatively greater D3:D2 receptor affinity ratio compared to endogenous dopamine), there may be intra-subject variability among them [Table 2]. Therefore, failure of one agent should not preclude attempts at another. There are differences in duration of effect: 24-hour rotigotine patch>followed by extended release pramipexole>extended release ropinirole>pramipexole>ropinirole>L-dopa. L-dopa, however, is the most rapidly absorbed, and therefore may be considered for as-needed use.

## Augmentation

The long-term use of DA for RLS is more problematic, as some subjects develop tolerance and others can develop very problematic augmentation [87•].



Augmentation is defined by an earlier phase shift of symptom onset, an increased intensity of symptoms, increased anatomic involvement, or less relief with movement [111]. Levodopa has the worst augmentation, often within six months, and is much less used because of this problem [112]. Augmentation with dopamine agonists is modest at one year (2–9 %), but seems to increase linearly over time [113–116]. There is some open label non-controlled data suggesting that the rotigotine patch may have less augmentation than oral agents [115]. Whether this results from preventing the actual physiologic process of augmentation, or by intrinsically treating augmentation by already having medicine in the system during the day, is not known. Risk factors for augmentation have been inconsistent, but include lower serum ferritin, a higher dose of a dopaminergic, worse RLS, a family history of RLS, and absence of neuropathy [112, 117, 118].

Although augmentation has been highly associated with dopaminergics, despite a few case reports seen with other classes of agents, only recently has a study confirmed that augmentation was higher with pramipexole (0.5 mg) than with the non-dopaminergic pregabalin at 52 weeks, although this study was complicated by a very high dropout rate [113].

The mechanisms behind augmentation are still not understood and there is no standard treatment strategy to address it. Taking the DA earlier, fractionating the dose, or switching to a longer-acting DA and taking it earlier will usually treat earlier onset RLS symptoms initially, but the augmentation may continue to worsen over time. Eventually, stopping the offending agent may be necessary, but is very difficult to accomplish without a severe exacerbation of symptoms. This usually lasts 1–2 weeks, then subsides and the RLS reverts back into the baseline nocturnal symptoms. In our experience, only high potency narcotics can treat this withdrawal phase.

## Alpha-2-delta ligands

Gabapentin and pregabalin have affinity for the alpha-2-(delta) sub-unit of the sodium channel. Both have been used to treat seizures and various painful conditions. Gabapentin enacarbil (an extended release preparation of a gabapentin precursor with markedly improved absorption throughout the gastrointestinal tract) [119, 120] and pregabalin have both improved RLS symptoms in large, Class I, controlled, multi-center trials [121–125]. Smaller studies also support the use of relatively high dose gabapentin [126]. Gabapentin enacarbil is approved by American agencies, but pregabalin is not, despite similar efficacy results. Compared to DA, these drugs show more improvement of sleep architecture, mostly by increasing the percentage of slow wave sleep, but with less improvement of PLMS. Overall efficacy on the IRLS tends to be similar when comparing different trials. One large comparator trial that did directly evaluate high dose pregabalin vs. lower dose pramipexole found that at 12 weeks, both groups were superior to placebo, but not significantly different from each other [110]. There was a trend favoring pregabalin, but also a higher dropout rate due to adverse events.

Both DA and alpha-2 delta ligands are considered first line therapies for RLS. Anecdotally, the alpha-2 delta agents better improve associated painful conditions and sleep, whereas DA may better improve pure urge

to move and PLMS (motor component of RLS). Therefore, the specific RLS phenotype and associated conditions may be considered when picking an agent. Combined use has not been formally studied, but is common in practice. Of note, it is difficult to switch directly from a DA to an alpha-2 delta ligand in the setting of augmentation, as they tend not to adequately treat symptoms unless there has been a washout period in between the DA and the alpha-2-delta drug.

## Opioid medications

Opioid medications, also known as narcotics, have long been known to successfully treat RLS. Open label trials consistently demonstrate good initial and long-term results, without difficulty with tolerance, dependence or addiction [127]. There exist, however, only a modest amount of controlled data that demonstrate efficacy [128, 129]. In one recent, well-designed large placebo controlled trial, prolonged release oxycodone-naloxone was evaluated [130]. The dose of oxycodone ranged from 10 to 40 mg/day in two divided doses, and was titrated to effect. Improvement at 12 weeks was 7 points (IRLS score) superior to placebo and adverse events are what would be expected with an opioid (nausea, sedation, constipation). Intrathecal spinal morphine pumps have also been used in severe refractory cases [131].

There is impressive long-term, open label data with methadone (a  $\mu$  specific opioid agonist) in RLS patients who have failed dopamine agonists due to lack of efficacy, adverse events, or severe augmentation [132, 133]. Overall, methadone at doses from 5 to 20 mg/day (often about 10 mg/day) markedly benefits most refractory RLS patient without augmentation, tolerance, or evidence for dependency. Patients taking methadone dropped out within the first three months due to expected side effects, but for those who initially tolerated the medication, long-term tolerability and efficacy was excellent.

Interestingly, there is some evidence suggesting the effect of opioids is independent of their analgesic effect, although a detailed understanding is lacking [134]. Mu-opioid drugs, which potentiate dopamine release and up-regulate dopamine receptors, all appear effective, whereas Kappa receptor drugs, like meperidine, that inhibit dopamine release are not effective [135]. Overall, opioid medications may be underutilized when managing chronic and severe RLS.

## Iron

Although open label oral iron supplementation has been reported to improve RLS, there is very little controlled data for oral iron supplementation, which has not significantly improved RLS in trials [136, 137]. In some of these reports, however, the oral iron did not markedly increase iron levels, and this fact highlights the limitations related to absorption and tolerance. Many different iron salts and organic preparations exist. Tolerability and absorption may vary among them, but no formal data support superiority of any preparation. It is also ideal to take oral iron without other foods or divalent metals. It is generally recommended to take oral iron supplements with RLS, especially if iron studies

[ferritin (<50) or iron binding percentage (<20 %)] is even modestly low, but there is surprisingly little formal data. Oral iron can cause constipation, bloating, and other abdominal discomfort, and so is sometimes poorly tolerated.

Intravenous iron markedly increases iron stores and has been studied in both RLS with and without iron deficiency. Results are mixed, but mostly support the use of some intravenous iron preparations. Both rational explanations and empirical data specifically support the use of iron dextran for RLS. This preparation stays in the serum longer than other preparations, and it appears to take days to transport the iron into the CNS, where it presumably is treating RLS. High molecular weight iron dextran has been most associated with anaphylactic reactions, but this does not seem to occur with low molecular weight preparations, which are now recommended [138]. The most commonly prescribed dose is 1 gm. A controlled trial of iron sucrose (a common preparation) failed to show benefit [139]. Intravenous iron is increasingly used to treat RLS, especially refractory cases. Concerns about toxic effects of very high intravenous dosing are reasonable, but to date no animal data suggest dangerous effects of this treatment.

### Miscellaneous treatments

Despite their past widespread use, there is little data to support the use of benzodiazepines for RLS. In the opinion of most experts, benzodiazepines do help facilitate sleep, but seldom improve RLS cardinal features. These can be used successfully in mild cases of RLS and as adjunct therapy for residual insomnia.

Numerous other agents, including other anti-epileptic and muscle relaxant medications, such as levetiracetam, carbamazepine, clonidine, baclofen, tramadol, and magnesium, have been reported to help RLS, but suffer from limited data and cannot be recommended as either first-line or second-line therapy.

Physical measures that increase activity or create a sensory stimulus [140] can also improve RLS, but are often problematic when one desires sleep. One such vibrating device was recently approved by American agencies for RLS treatment. General exercise and stretching techniques are also advocated. Botulinum toxin injections into leg muscles are not effective [141]. Deep brain stimulation (DBS) into the thalamic ventral intermediate nucleus [142] does not help, but a single case of DBS into the globus pallidus internus (GPi) showed benefit [143].

### Treatment of RLS in specific populations: pediatrics and renal failure

The treatment of pediatric RLS is much less studied. In open label reports and anecdotally, both oral and intravenous iron often improve symptoms, much more consistently than in adult RLS [144–147]. We recommend aggressive oral iron treatment in this population. A single controlled trial supports the use of L-dopa [148]. Anecdotal experience also supports the use of gabapentin.

Uremic RLS seems to respond to similar medications as idiopathic RLS [149]. Anecdotally, higher doses of medications are often required to achieve remission. Successful kidney transplant is the definitive treatment.

## Compliance with Ethics Guidelines

### Conflict of Interest

William G. Ondo reports grants and personal fees from Lundbeck, USWorld Meds, and Merz, as well as personal fees from Avanir, TEVA, UCBPharma, and Xenoport, outside the submitted work.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

## References and Recommended Reading

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