Restless legs syndrome

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Abstract | Restless legs syndrome (RLS) is a common sensorimotor disorder characterized by an urge to move that appears during rest or is exacerbated by rest, that occurs in the evening or night and that disappears during movement or is improved by movement. Symptoms vary considerably in age at onset, frequency and severity, with severe forms affecting sleep, quality of life and mood. Patients with RLS often display periodic leg movements during sleep or resting wakefulness. RLS is considered to be a complex condition in which predisposing genetic factors, environmental factors and comorbidities contribute to the expression of the disorder. RLS occurs alone or with comorbidities, for example, iron deficiency and kidney disease, but also with cardiovascular diseases, diabetes mellitus and neurological, rheumatological and respiratory disorders. The pathophysiology is still unclear, with the involvement of brain iron deficiency, dysfunction in the dopaminergic and nociceptive systems and altered adenosine and glutamatergic pathways as hypotheses being investigated. RLS is poorly recognized by physicians and it is accordingly often incorrectly diagnosed and managed. Treatment guidelines recommend initiation of therapy with low doses of dopamine agonists or $\alpha_2\delta$ ligands in severe forms. Although dopaminergic treatment is initially highly effective, its long-term use can result in a serious worsening of symptoms known as augmentation. Other treatments include opioids and iron preparations.

Restless legs syndrome (RLS) is a sleep-related sensorimotor disorder with an unclear pathophysiology. RLS is characterized by an urge to move that occurs during rest or is exacerbated by rest, occurs in the evening or night and disappears or improves with movement. RLS was initially described by Sir Thomas Willis in the seventeenth century[1], as an akathisiac (that is, characterized by a feeling of restlessness and an urge to move) psychiatric disorder, and then by Ekbom with an extensive and detailed clinical connotation that established its neurological nature[2]. These factors account for the alternative proposed name of Willis–Ekbom syndrome.

Although RLS is highly prevalent in the general population, symptoms vary considerably in terms of frequency (from occurring less than once per year to daily) and severity (from mildly irritating to disabling with severe effects on sleep, quality of life (QOL) and mood, and, in very severe cases, associated with increased risk of depression, suicide and self-harm)[3]. RLS age at onset has a bimodal distribution, with one peak at around 20 years of age and a second peak at around 40 years of age, although most patients are diagnosed from the fourth to the sixth decade of age[4–6]. Patients with early-onset RLS (by 40–45 years of age) more often report a positive family history of RLS and a slowly progressing course of the disorder compared with patients with late-onset RLS (after 40–45 years of age), who have a more rapid course of the disorder and are more likely to have multiple comorbidities[4–6].

RLS is classified as primary (idiopathic) or secondary (symptomatic), depending on the presence of other disorders. Also, patients with RLS often have insomnia and involuntary periodic leg movements (PLM) occurring in sleep (PLMS) or resting wakefulness (PLMW). PLMS have been reported in at least 80% of patients with RLS, whereas PLMW are less characteristic and so PLMW have received less attention from the scientific community[7].

Awareness of RLS is poor, with low recognition among physicians, and difficulty for patients in describing their symptoms and understanding which specialist to be referred to. Accordingly, diagnosis is often delayed for years or is confounded with primary insomnia, so this disorder is often not treated or is improperly treated for a long time[8]. Owing to its inadequate diagnosis and treatment, in addition to its high prevalence, the socio-economic costs of RLS are high[9]. Long-term management for moderate-to-severe RLS is mandatory, as RLS is frequently a lifelong disorder.

This Primer summarizes the epidemiology, mechanisms, pathophysiology, diagnosis and management of RLS. This Primer also discusses the QOL issues faced by patients with this syndrome, and touches upon future directions and unanswered clinical and research questions.

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Epidemiology

Development of the so-called RLS minimal diagnostic criteria by the International RLS Study Group (IRLSSG) in 1995 (REF.[10]), and its subsequent adaptations until 2014 (REF.[7]) (BOX 1), enabled the assessment of RLS prevalence in population and clinical studies. The prevalence of RLS varies considerably according to methods of diagnosis, country, sex, age and comorbidity burden, which impedes comparisons between studies[11]. In addition, differences in health behaviours, genetic risks, disease awareness and perception also contribute to the reported variations in prevalence[12].

The prevalence of RLS is low in most Asian populations, varying between 1% and 3%[13–15]. By contrast, prevalence is considerably higher in Europe and North America, ranging from 5% to 13% in most population-based studies[12]. Few studies have been conducted in other regions, but the available studies also reported a low prevalence in the respective populations[16]. In one of the few studies, a similar prevalence of RLS was found in white and black individuals in Baltimore, USA[17]. At the population level, only three longitudinal studies have been published with reported incidences of between 9 and 22 cases per 1,000 person-years of follow-up and a persistence of symptoms over time in around 50% of individuals in Japan and Germany[18,19].

RLS affects women more frequently than men, with a reported 30–50% higher prevalence in women[20]. Women should to be asked about RLS during pregnancy because it occurs in one in five pregnant women, which is a two-fold to threefold higher prevalence than in the general population[21]. RLS symptoms peak in the third trimester of pregnancy and resolve around childbirth[22]. However, RLS can reappear later in life, with around a fourfold higher chance than women who did not experience RLS during pregnancy[23].

In most studies, the prevalence of RLS increases with age, with typical onset in the thirties or forties in adults, but onset can also occur in children. However, studies of paediatric RLS are rare; the few reports from the USA, UK, Turkey and China found a prevalence of 0.5–1.0% for moderate-to-severe symptoms[12]. Interestingly, the sex difference in the prevalence of RLS is not observed until late adolescence[24].

Studies in individuals with a high comorbidity burden, such as studies conducted in primary care practices, have a consistently observed higher prevalence of RLS than studies of healthy individuals[25]. Moreover, a growing number of publications have reported associations between RLS and numerous diseases (BOX 2), including metabolic conditions (diabetes mellitus and iron deficiency) and cardiovascular or renal disorders, and arterial hypertension, autoimmune diseases (such as multiple sclerosis), polyneuropathy, neurodegenerative disorders (such as Parkinson disease), and conditions associated with inflammation and depression[26]. However, most of the studies that reported these associations were cross-sectional and, therefore, could not identify whether RLS or the comorbid condition had begun first. Few longitudinal studies into RLS have been carried out, but two studies found that a multimorbidity index that included several conditions increased the risk of incident RLS with each additional comorbidity[25].

Risk factors

Research into the role of lifestyle factors in the onset of RLS has increased over time, as lifestyle factors offer a high potential for prevention. Several studies found protective effects of physical activity, whereas the effect of obesity and smoking yielded inconclusive results[27]. Genetic predisposition is an essential contributor to RLS.

Genetic risk factors. A positive family history of RLS is found in 20–60% of patients, depending on the study, and is believed to vary by differences in ethnicity, study design and sample size. Of note, a positive family history can be found in up to 60% of individuals with idiopathic RLS and up to 80% of monozygotic twins[28–30]. In familial RLS, symptoms tend to start earlier in life than in

Box 1 | **Diagnostic criteria for RLS**[7]

Essential criteria

1. An urge to move the legs that is usually accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs (or sometimes other body parts).
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur at night or are worse in the evening or night than during the day.
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioural condition (such as myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort or habitual foot tapping).

Supportive criteria

1. Periodic limb movements (PLM): presence of periodic leg movements in sleep (PLMS) or resting wakefulness (PLMW) at rates or intensity greater than expected for age or medical/medication status.
2. Dopaminergic treatment response: reduction in symptoms at least initially with dopaminergic treatment.
3. Family history of restless legs syndrome (RLS) among first-degree relatives.
4. Lack of profound daytime sleepiness.

Box 2 | **Frequent comorbid conditions associated with RLS/PLMS**

Major associations

- Renal failure (end-stage renal disease requiring haemodialysis)
- Iron deficiency
- Pregnancy

Other associations

- Drug/substance use
  - Neuroleptics
  - Histamine-receptor antagonists
  - Lithium
  - Antiepileptics
  - Antidepressants
  - Antiemetics
  - Alcohol
- Neurological disorders
  - Polyneuropathy
  - Migraine
  - Amytrophic lateral sclerosis
  - Myelitis
  - Syringomyelia
  - Multiple sclerosis
  - Spinocerebellar ataxia
  - Myasthaenia gravis
  - Tourette syndrome
  - Neurodegenerative disorders (such as Parkinson disease or multiple system atrophy)
  - REM sleep behaviour disorder
  - Narcolepsy
- Rheumatological disorders
- Hypoxic conditions
  - Chronic obstructive pulmonary disease
  - Obstructive sleep apnea syndrome
  - High-altitude/mountain sickness
  - Sarcoidosis
  - Pulmonary hypertension
  - Lung transplant
- Cardiovascular disorders (such as hypertension)
- Obesity
- Diabetes mellitus

PLMS, periodic leg movements in sleep; RLS, restless legs syndrome.

sporadic RLS, with a mean onset before 30–40 years of age, and often with a dominant mode of inheritance[4,31]. Nevertheless, RLS in general can appear at any age, with later cases more often associated with a more severe and rapid course of the disorder[32].

Individual genetic risk variants for RLS remained elusive until genome-wide association studies (GWAS) became feasible in 2007 (REFS[33,34]). Earlier linkage studies had identified several linked regions but no causal genes for supposedly monogenic RLS[35]. Moreover, studies using exome sequencing or whole-genome sequencing were limited to a few families, failed to identify unequivocal causal genetic variants and lacked confirmation in independent studies[36–39]. By contrast, large-scale GWAS identified definite genetic risk variants and nominated genes for functional follow-up[33,34,40–42]. To date, these GWAS have uncovered and replicated 23 common genetic risk variants in 22 genomic loci[40]. The first of the two most recent GWAS meta-analyses yielded 20 genome-wide significant risk variants, and pathway analysis implicated neurodevelopmental processes in the pathophysiology of RLS. Moreover, this study estimated the heritability contributed to RLS by common variants (single-nucleotide polymorphism (SNP)-based heritability) to be 19.6%, providing a measure of the importance of these variants in RLS susceptibility[40]. The second GWAS confirmed the known loci and identified three novel risk loci for RLS. In addition, an expression quantitative trait loci (eQTLs) analysis revealed significant *cis*-eQTL effects in this dataset, thereby suggesting candidate causal genes in four risk loci[42].

Identification of causal genes in GWAS risk loci is challenging. Two studies have addressed this task. One transcriptome-wide association study (TWAS, which integrated RLS GWAS summary statistics and publicly available genome-wide gene expression data) yielded five candidate genes in known loci as well as six novel genes[43]. In another study using a more focused approach, targeted sequencing of 84 genes in known RLS risk loci was carried out and identified 14 candidate causal genes by testing for a significant burden of rare coding variants[44]. Taken together, these studies have substantiated the involvement of both common and rare genetic variants in RLS susceptibility in populations of European ancestry. Further variants will be identified, because the GWAS discovery sample size (10,000–15,000 individuals) is still relatively small, and rare and structural variants have not yet been assayed at a genome-wide level. To date, populations of non-European ancestry have not been well studied. Few genetic studies have been carried out in Asian individuals, although these studies were of small sample size and have only validated single SNP associations, for example, for *BTBD9* and *PTPRD*, but not for *MEIS1*, the latter of which is the top hit in all European ancestry studies[13,45].

These genetic findings have led to new animal and cellular models of RLS. In-depth functional studies have mainly focused on three genes: *MEIS1*, *BTBD9* and *PTPRD*. Bioinformatic pathway and gene set enrichment analyses across the 19 risk loci identified processes such as neurogenesis, axon guidance and synaptogenesis, which are important for the correct building and maintenance of functional neuronal circuitry in the nervous system[40] (BOX 3).

Interestingly, GWAS of insomnia symptoms also identified strong associations with variants in *MEIS1* (REFS[46,47]). In addition, genetic correlation analyses of these GWAS and those for RLS showed a significant positive correlation of the overall association signals for RLS and insomnia symptoms[47–49]. Further statistical analyses indicated that the association between *MEIS1* and insomnia symptoms is likely to be driven by the presence of a subgroup of individuals with comorbid RLS. This finding was corroborated by a negative GWAS of the same variant in a population of patients clinically diagnosed with insomnia[47]. Other risk loci that are shared between RLS and insomnia symptoms, statistical analyses pointed to possible pleiotropic effects (that is, shared pathomechanisms)[49,50]; however, additional studies in large and carefully phenotyped cohorts are needed to enable definite conclusions.

Mechanisms/pathophysiology

Although its aetiopathogenesis still remains somewhat uncertain, RLS is considered a complex condition in which genetic background, environmental factors and gene–environment interactions predispose people to disease and affect expression of the full clinical phenotype[26]. In terms of aetiological insights, several mechanisms have been identified and proposed to play a major part in pathophysiology, and some of these can be targets for therapeutic action (FIG. 1).

Brain iron deficiency

Numerous studies have indicated a high prevalence of RLS symptoms in individuals with conditions associated with insufficient iron availability[51]. For example, the prevalence of RLS symptoms in individuals with iron

deficiency is 30%[52], around four to six times higher than in the general population, depending on sex.

Of note, most patients with RLS do not have systemic iron deficiency but rather have brain iron deficiency. Whether all patients with RLS have brain iron deficiency is unknown; however, transcranial ultrasound of the substantia nigra (the main iron store in the brain) found hypoechogenicity, which is supposed to indicate a decreased iron content, with specificity up to 0.90, and sensitivity to 0.82 (REFS[53,54]). Magnetic resonance imaging (MRI) studies have showed decreased iron in the red nucleus in patients with RLS[55]. Brain iron deficiency in patients with RLS has also been shown by reduced cerebrospinal fluid (CSF) levels of ferritin (the intracellular iron storage protein) and increased CSF transferrin levels (the extracellular iron carrier protein) with normal serum levels of ferritin and transferrin[56]. Furthermore, post-mortem studies have shown alterations in expression of proteins involved in iron management and regulation in the choroid plexus and in the brain microvasculature, namely, a significant reduction of intracellular iron and ferritin and an upregulation of transferrin receptor of patients with RLS, suggesting altered brain iron acquisition[57]. Moreover, the alteration of transferrin receptor, ferritin and the transporters DMP1 and ferroportin (a cellular iron exporter) in brain endothelial cells support that iron transport to the brain via transferrin, which is regulated by endothelial cells in the blood–brain barrier, is impaired in RLS. Altogether, brain iron deficiency in RLS may result from alterations of iron acquisition by the brain[57].

Box 3 | **Genetic risk factors for RLS**

MEIS1, which is the strongest identified genetic risk factor for restless legs syndrome (RLS)[46,204] encodes the TALE homeodomain transcription factor MEIS1, which is an important regulator of cellular proliferation and differentiation during development[205–207]. RLS-associated variants of *MEIS1* affect gene activity during embryonic development, specifically in the ganglionic eminences, which are developmental structures that give rise to a diverse population of neurons, including precursors of basal ganglia cells[208]. This change in MEIS1 activity may conceivably cause subtle but pathogenically important changes in the timing of differentiation of basal ganglia cells. These could in turn result in differences in the number, type and localization of cells in the central nervous system, possibly affecting the sensorimotor circuits thought to be involved in RLS[49].

PTPRD, which is also located at an RLS risk locus, is involved in neurodevelopment[209]. RLS-associated variants in *PTPRD* have been linked to its expression level and a knockout mouse model showed behavioural changes such as increased locomotion and reduced sleep during the sleep onset period[210]. Similar changes in locomotor behaviour and sleep have been observed in mouse and *Drosophila* knockout models of *BTBD9* (REFS[211–213]). *BTBD9*-knockout mice also have changes in neural circuitry patterns, such as higher neural activity in the striatum, with stronger postsynaptic currents in medium spiny neurons and decreased excitability of striatal cholinergic interneurons[211].

Model systems for MEIS1 and BTBD9 have also been used to evaluate brain or systemic iron and dopamine metabolism[46,204,211,214,215]. Reduced expression of MEIS1 affected iron and metal metabolism gene expression and resulted in increased ferritin expression in *Caenorhabditis elegans* models and in human cell lines[46,214]. By contrast, increased iron levels were found in the serum, but not in the striatum, of *BTBD9*-knockout mice[211]. The same mouse line showed circadian-dependent reduction of dopamine receptor D2 (D2R) expression in the striatum[215]. One small proteomic study evaluating serum biomarkers of RLS identified five possible interesting protein interaction networks, of which one related to brain-related development[216]. How these neurodevelopmental changes relate to the longstanding pathogenetic hypotheses for RLS remains to be determined.

Serum ferritin and transferrin saturation (percentage iron binding) are the best easily available markers of iron deficiency, although other markers may be useful in this regard. For example, serum levels of hepcidin (one of the master regulators of iron homeostasis) was higher in drug-free patients with primary RLS than in controls, and seems to be associated with RLS clinical severity[58]. In addition, higher hepcidin levels were associated with older age, later RLS onset, less daytime sleepiness and familial RLS[59]. These results suggest that serum hepcidin may be an interesting biomarker for RLS, and may be more relevant than ferritin owing to complex peripheral iron metabolism deregulation in RLS.

Dopamine dysregulation

Involvement of the dopaminergic system in the pathophysiology of RLS is supported by the therapeutic benefit of dopamine agonists on both sensory and motor (PLMS) symptoms. These clinical observations are suggestive of diminished dopaminergic signalling in RLS; however, subsequent research found increased synthesis and release of dopamine, which is compatible with a presynaptic hyperdopaminergic state[60]. Indeed, patients with RLS have reduced f-DOPA uptake[61], increased tyrosine hydroxylase (TH, which is involved in dopamine synthesis) staining in the substantia nigra and the putamen, decreased dopamine transporter (DAT, involved in dopamine uptake from synaptic clefts in the putamen), increased CSF biopterin (a cofactor involved in dopamine synthesis), increased CSF 3-*O*-methyldopa (3OMD, a metabolite of the dopamine precursor l-dopa), decreased dopamine 2 receptor (D_2R) in the morning, and mildly increased D_2R in the afternoon in the putamen[55]. Interestingly, brain iron deficiency in rodents confers a similar dopaminergic profile to that observed in patients with RLS, that is, a decrease in striatal D_2R density, decreased DAT in the putamen and increased expression of phosphorylated TH in the substantia nigra[55,62]. The mechanism of action of dopaminergic medications in RLS is unclear, owing to the reported hyperdopaminergic state; however, it may be partially explained by the circadian aspect of dopaminergic physiology; a postsynaptic downregulation of D_2Rs may lead to a night-time dopaminergic deficit[63]. In addition, the dopamine receptor agonists pramipexole and ropinirole block glutamate release in rats with brain iron deficiency and controls[64], suggesting dopamine receptors in striatal glutamatergic terminals might be one of the targets for these drugs in RLS[64].

In addition to central dopaminergic mechanisms, the descending spinal dopaminergic system (which originates from A11 neurons in the dorsal-posterior hypothalamus) might also be involved in the pathophysiology of RLS. Indeed, lesioning of the A11 descending projections in animals may cause RLS symptoms[65]. For example, mice with lesions of the A11 region have increased volitional movement, greater activity and aggressive behaviour, which is further accentuated by iron deprivation[66]. However, no damage of the A11 region was found in six brains from patients with idiopathic RLS[67].

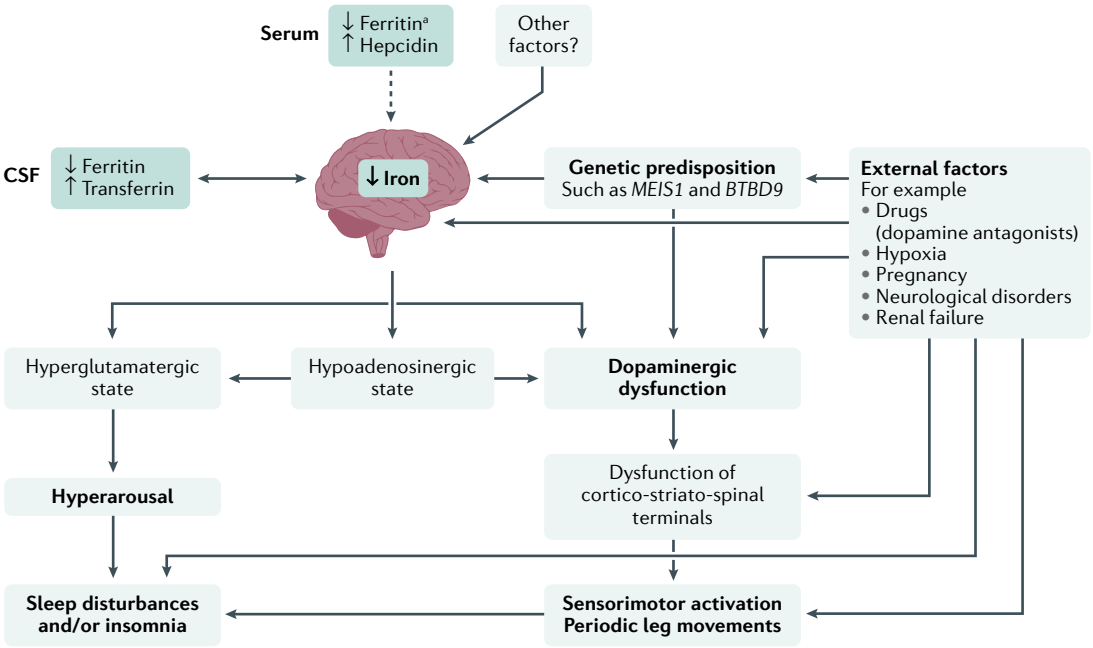

Fig. 1 | **Proposed pathogenetic model of RLS.** The primary pathology of restless legs syndrome (RLS) may relate to brain iron deficiency that might induce hyperdopaminergic and hyperglutamatergic states. Such interplay between brain iron and neurotransmitters may trigger the arousal systems, leading to sleep disturbances, and alter the functioning of the corticostriatal circuits, leading to the sensorimotor symptoms of RLS. Interactions between genetic predisposition and external factors may also be involved in pathophysiology. Other factors may also be involved, but remain to be identified. CSF, cerebrospinal fluid. [a]A drop in serum ferritin is seen only in 10–20% of patients with RLS.

Of note, the dopaminergic and brain iron deficiency hypotheses of RLS may not be mutually exclusive. Animal models of brain iron deficiency lead to changes in striatal dopaminergic function, and in patients with RLS, biochemical, post-mortem and imaging studies also suggest that alterations in iron trafficking to the brain lead to changes in striatal dopamine neurotransmission[68]. Furthermore, one study found a significant reduction in haem oxygenase 1, mitoferrin 1 and mitoferrin 2 mRNA in peripheral blood monocytes from patients with RLS, indicating a mitochondrial iron deficiency with associated impairment of mitochondrial function in these patients. Of note, the impaired mitochondrial respiratory capacity partly improved after treatment with dopaminergic therapies, suggesting the involvement of dopamine in cellular iron homeostasis[69].

μ-opioid receptors mediate both the analgesic and addictive effects of opioids. These receptors are located in the dopaminergic ventral tegmental area and in the nucleus accumbens, and are probably also involved in the therapeutic effects of opiates in RLS. Thus, agonists of μ-opioid receptors ultimately lead to dopaminergic activation[70].

Hyperglutamatergic state

Several studies have supported a role for altered glutamatergic neurotransmission in RLS. For example, one study using magnetic resonance spectroscopy found an increase in basal glutamate levels in the thalamus in patients with RLS compared with controls[71]. Moreover, therapies that have an effect on RLS symptoms affect glutamate receptors or glutamate release, such as $\alpha_2\delta$ ligands (which inhibit presynaptic glutamate release[61,72]) and drugs that inhibit NMDA receptors (ketamine and methadone)[73–75] or AMPA-glutamate receptor (perampanel)[76]. Indeed, drugs that inhibit glutamate receptors are probably more effective in improving sleep duration than dopamine receptor agonists, whereas the reverse is true for reducing PLMS[72]. Indeed, dopaminergic receptor agonists were associated with a low improvement of sleep efficiency, despite the pronounced improvement in PLMS and sensory symptoms[69,77]. Of note, iron deficiency might lead to hypersensitivity of the glutamatergic cortico-striatal terminals in rodents[64,78,79].

Role of adenosine

In rodents, brain iron deficiency produces a significant downregulation of adenosine A_1 receptors (A_1R) and an upregulation of striatal A_2A receptors (A_2AR), leading to increased sensitivity of cortico-striatal glutamatergic terminals[80,81]. A_1R and A_2AR are localized to cortico-striatal terminals, where they form A_1R–A_2AR heteromers that (in low adenosine concentrations) inhibit glutamate release and (in high adenosine concentrations) facilitate glutamate release[82]. However, A_1R is more sensitive to brain iron deficiency than is A_2AR[80], so it is likely that brain iron deficiency would first induce an A_1R downregulation before upregulating A_2AR, leading to a hypoadenosinergic state.

In addition to effects on glutamate release, A_1R and A_2AR interact with dopamine D_1 receptors (D_1R) and D_2R, forming A_1R–D_1R and A_2AR–D_2R heteromers, respectively[83]. These A_1R–D_1R and A_2AR–D_2R heteromers are highly expressed on the striatonigral and

striatopallidal neurons and may exert an elaborated inhibitory modulation of dopamine signals that finally disrupts the adenosine–dopamine–glutamate balance in the striatum[83]. In support of a role for adenosine in RLS, an open study found that dipyridamole (a blocker of the adenosine reuptake transporters ENT1 and ENT2, thereby increasing extracellular levels of adenosine in the brain) had a therapeutic effect on sensory symptoms, PLMS and sleep disturbances in patients with RLS; these findings were replicated in a crossover, placebo-controlled study[84,85].

Neurophysiology

Neurophysiological studies of RLS have been used to obtain indirect measures of the central and peripheral nervous system excitability, and to probe involved neural circuits[86]. These findings are in line with those using neuroimaging in RLS.

Overall, electrophysiological data support the hypothesis that RLS is a complex sensorimotor disorder in which cortical, subcortical, spinal and peripheral nerve generators comprise a dysfunctional network that results in enhanced excitability, decreased inhibition and impaired synaptic plasticity[87]. Translationally, these results suggest that, in addition to the well-known dopaminergic involvement, other pathways (including glutamate, GABA and opioid pathways) may contribute to the pathogenesis of RLS, as in chronic pain conditions[88]. Notably, the reduced central inhibition can contribute to the excitation state of segmental spinal pathways more than a primary excitability increase can. Indeed, several transcranial magnetic stimulation studies demonstrated supra-spinal GABA-mediated disinhibition in RLS, which suggest that the cortex is not involved in generation of PLMS[89,90]. Moreover, abnormal peripheral nerve function may also affect spinal and supraspinal activity, as demonstrated by studies on the H-reflex, quantitative sensory testing, and the cutaneous silent period[91], although the findings from each technique should be considered within the whole pathophysiological scenario proposed for RLS.

Neuroimaging

Studies using cerebral MRI found an increased presence of silent cerebral microvascular disease and gliosis in patients with long disease duration of RLS, which is possibly associated with the suggested link between RLS and hypertension, stroke and other cardiovascular disease[92]. In addition, diffusion-tensor imaging studies have confirmed the presence of subtle white-matter changes, particularly in patients with severe symptoms of RLS, in regions affecting structures involved in sensory or motor control, and sensorimotor integration, indicating possible dysfunctional integration of these networks in RLS[93]. Moreover, several studies suggest that decreased functional connectivity in the dopaminergic network in RLS is an expression of sensorimotor processing dysfunction that involves nigrostriatal, mesolimbic and mesocortical connections, and is accompanied by an increased functional connectivity in the thalamus (ventral lateral, ventral anterior and ventral posterior lateral nuclei, and the pulvinar)[94]. Another study using multimodal MRI further confirmed the involvement of white matter in RLS (specifically the post-central and precentral cortex and the frontopontine tract), and correlated white-matter involvement with disease duration, in addition to increased grey-matter volume in the right primary motor cortex (negatively correlated with the above frontopontine tract changes)[95]. In addition, iron content was reduced in the putamen and the temporal and occipital areas of patients with RLS. The authors concluded that a progressive white-matter decline of somatosensory circuits, possibly supporting sensory leg discomfort, could be identified by multimodal MRI, in addition to increased grey-matter volume of the premotor cortex, possibly as a consequence of functional neuronal reorganization[95]. More recently, a case–control resting-state functional MRI study has found higher connectivity within salience, executive and cerebellar networks, and lower cerebello-frontal communication in patients with RLS than in controls[96]. In addition, this study found lower cerebello-parietal connectivity in untreated patients than in healthy controls, corresponding to regions associated with attention, response inhibitory control and sensory information processing[96]. Moreover, connectivity between the thalamus and frontal regions was significantly higher in patients using dopaminergic medications than in untreated patients and controls, suggesting a treatment effect on the thalamus[96].

Hypoxic pathway

Emerging evidence indicates the involvement of hypoxia in RLS pathogenesis. In accordance with these findings, a small number of epidemiological studies have reported an increased prevalence of RLS and, in one case, of PLMS, in populations living at high altitude[97–101]. Moreover, lung diseases associated with hypoxia, such as chronic obstructive pulmonary disease, sarcoidosis, asthma, pulmonary hypertension and obstructive sleep apnoea are risk factors for RLS[97,102].

Compared with healthy controls, patients with RLS show peripheral hypoxia, measured non-invasively on the skin of the legs[103]; in addition, symptom severity correlated with a high chest-to-foot oxygen gradient, and pramipexole improved both symptoms and peripheral hypoxia. Dopamine receptors are present in vascular endothelium and their binding causes vasodilatation, which potentiates peripheral blood flow[104]. Peripheral muscular microvascular abnormalities, such as capillary tortuosity, associated with lower predicted oxygen uptake were found in patients with RLS compared with controls[105]. Such remodelling of microvascular networks might represent angiogenesis as a physiological response to hypoxia, which is also supported by the finding of vascular endothelial growth factor (VEGF) upregulation in the skeletal muscles of the legs in patients with RLS[106]. Activation of the hypoxic pathway with upregulation of hypoxia inducible factor 1α (HIF1α) was found in the substantia nigra in a few brains from patients with RLS[107]. Hypoxia could not only upregulate the expression of HIF1 but also downregulate the expression of some iron-related proteins and the vascular endothelial growth factor[55].

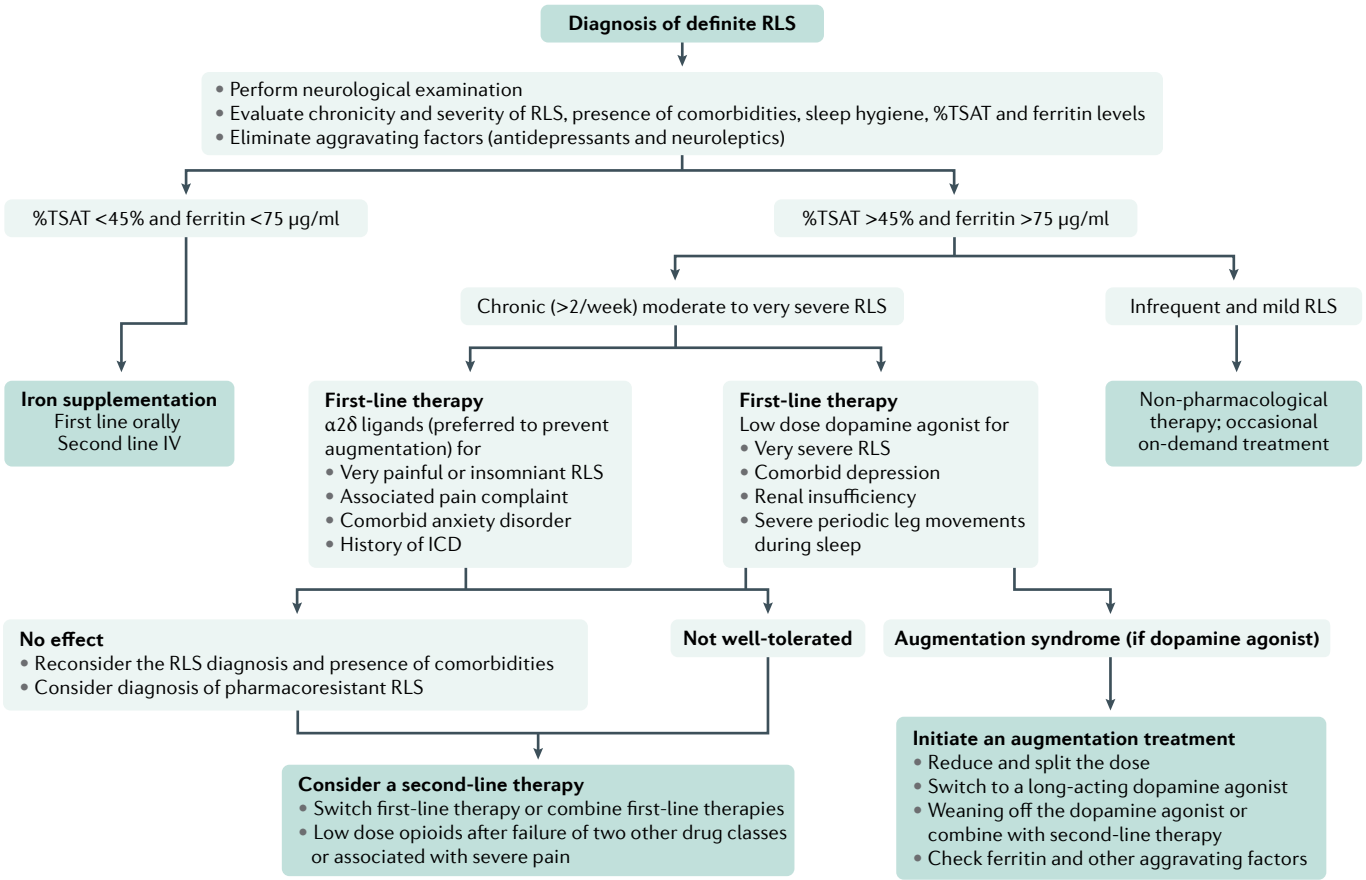

Fig. 2 | **Algorithm for management of RLS.** Treatment of restless legs syndrome (RLS) depends on the iron status of the patients and the severity and frequency of symptoms. ICD, impulse control disorder; TSAT, transferrin saturation.

Diagnosis, screening and prevention

Clinical evaluation and diagnostic criteria

The lack of a reliable biological diagnostic marker for RLS makes the clinical evaluation, particularly collecting the patient's medical history, a crucial step in correctly diagnosing this disorder, distinguishing symptomatic from idiopathic forms and guiding management. Diagnosis of RLS is based on proof of all five essential diagnostic criteria, ascertained through a detailed medical interview[7] (BOX 1) (FIG. 2).

RLS is characterized by an urge to move the legs that is usually, but not always, accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs. However, other body parts are involved in 30–50% of cases, particularly the arms, with different grades of symmetry[108,109].

Symptoms are usually reported as originating 'inside' or 'deep', from muscles or tendons;[7] however, some patients might have difficulty explaining their symptoms and may use strange or slang terminology. 'Pain' as well as possible references to thermal aspects of symptoms, are not infrequently used by patients[110]. However, 'restlessness' and 'urge to move' are probably the most appropriate terms to describe symptoms. Physicians may use incorrect words to describe symptoms, such as 'dysaesthesia' or 'paraesthesia', with the risk of overlapping with terminology used for peripheral neuropathy.

Symptoms start or worsen during periods of rest or inactivity (such as lying or sitting) and are partially or totally relieved by movement (such as walking or stretching), at least for as long as the activity continues[7]. Moreover, symptoms are common in certain situations, such as sitting in the car as a passenger, flying for long distances and sitting at the cinema or theatre. Although each patient has their own strategy to relieve symptoms, the most frequently reported are walking, stretching, massaging the affected limbs or other actions, such as showering the limbs with cold water or stepping on the floor with bare feet. By contrast, intense activity during the day may worsen the symptoms during the evening or night. More-severe RLS is associated with a shorter latency from rest or inactivity to symptom onset, as well as the reappearance of symptoms after the end of movement.

In most patients, symptoms are worse in the evening or night than during the day, or are only present during the evening or night[7,111]. However, in severe cases, symptoms can occur during the whole day. A careful evaluation might disclose whether the typical pattern was previously present in the patient medical history. The circadian trend of symptoms is critical in the differential diagnosis, and explains the effect of RLS on sleep initiation. The fluctuation of symptoms during the day is independent of activity, despite being modulated by activity, but correlates with core body temperature

and salivary melatonin levels, and is accompanied by a similar variation of the frequency of PLM[111–113].

The fifth diagnostic criteria was introduced in 2014 to rule out mimics and increase the specificity of the diagnosis[7]. Common mimics include positional discomfort, sore leg muscles, ligament sprain, tendon strain, positional ischaemia (numbness), dermatitis, bruising and, in children and adolescents, growing pains. Less common mimics include leg cramps, orthopaedic disorders, peripheral and spinal neurological disorders, muscle diseases, pain, drug adverse effects or haematological conditions. Of note, certain conditions can occasionally possess traits that meet four of the five inclusion criteria for RLS, such as leg cramps and positional leg discomfort (TABLE 1).

Although their presence is not mandatory for a diagnosis of RLS, other supportive criteria and associated clinical features are included in the diagnostic criteria. Some of these criteria, particularly, the effectiveness of dopamine agonists, lack of profound daytime sleepiness and presence of a family history of RLS contribute to a better characterization of the clinical picture of RLS, and help diagnosing uncertain and atypical cases (BOX 1).

Around 60–70% of patients with RLS experience disrupted sleep, including difficulties in falling asleep, reduced total sleep time and increased number of awakenings with RLS symptoms[114,115]. RLS-related insomnia mainly occurs during the first part of the night and sometimes represents the major complaint of patients, who may under-evaluate or not focus their attention on sensory symptoms. The high prevalence of disrupted sleep in patients with RLS, and the finding that 10% of patients with insomnia also report RLS symptoms, justifies a screening for RLS in all patients complaining about insomnia[116]. Conversely, all patients with suspected RLS should be questioned about the presence of insomnia. Sleep disruption in RLS might be refractory to common hypnotics and might persist even after successful treatment of sensory symptoms[117]. Importantly, despite sleep disruption and/or restriction in patients with RLS, they may lack daytime sleepiness, or at least, the level of sleepiness often seems disproportionate to the grade of night-time sleep impairment[118]. Other signs of chronic sleep deprivation such as fatigue, difficulty concentrating or depressive symptoms, may occur, but they are infrequently accompanied by profound sleepiness and needing to nap[71]. Severe sleepiness in patients with RLS should be investigated for other causes, such as sleep apnoea, medication or central hypersomnolence disorders.

Once diagnosed, several steps should be undertaken to evaluate the course and severity of RLS and to identify secondary or symptomatic forms. When untreated, RLS can be classified as 'chronic-persistent' if symptoms have occurred on average at least twice weekly for the past year, or as intermittent if they have occurred on average less than twice weekly for the past year, with at least five lifetime events[7]. Severity is routinely addressed using the International RLS (IRLS) rating scale, which consists of ten questions rated from 0 to 4, and is administered face-to-face. This scale classifies RLS as mild (scores 1–10), moderate (scores 11–20),

Table 1 | **Description of the main mimics and main differential features of RLS**

Disorder	Location and characteristics of the distress	Motions or movements that can relieve symptoms	Findings from neurological evaluation, and electromyography	Is there a circadian pattern of symptoms?	Is there a response to dopamine agonists?	Additional features
RLS	Diffuse unpleasant sensations that usually occur in the calf	Walking or altering position	Normal	Yes	Yes	Frequent familial history and/or association with iron deficiency
Sleep-related leg cramps	Painful involuntary muscle contractions that generally affect muscles in the calf or foot	Massaging or stretching the involved muscles	Normal	No	No	Muscular contraction can be palpable or visible. In some patients, muscle contraction can be secondary to another disorder.
Positional leg discomfort	Unpleasant sensations in the legs that are caused after sitting or lying in the same position for a long time	Changing position	Normal	No	No	None
Akathisia	Feeling of inner restlessness not exclusively located in legs	Movement	Normal	No	No	History of neuroleptic medication use or associated extrapyramidal symptoms
Polyneuropathy	Painful burning sensations in the upper and lower extremities (sometimes in a glove and stocking distribution)	None. However, inactivity can worsen symptoms	Altered (except occasionally in individuals with small-fibre polyneuropathy)	No or weak	No	None, or the urge to move the legs is less common than in RLS
Venous disorder	Sensory discomfort in the legs when standing	Resting or elevating legs	Normal	No	No	Skin alterations in some patients

RLS, restless legs syndrome. Data from REF.[203].

Table 2 | **Scoring of periodic leg movements during sleep and wakefulness in the WASM and AASM criteria**

	WASM criteria[124]	AASM criteria[123]
Inter-movement interval	Onset-to-onset: 10–90 s	Onset-to-onset: 5–90 s
Number of leg movements	Four or more[a]	Four or more
Inter-movement interval >90 s	PLM series stops	PLM series stops
Inter-movement interval <5 s	Not applicable	Counted as one leg movement
Inter-movement interval <10 s	PLM series stops	Not applicable
Sleep–wake periods	All leg movements form PLM series; for PLMS, only those during sleep are counted; for PLMW, only those during wakefulness are counted	Only leg movements during sleep form PLM series and are counted
Bilateral leg movements	Offset-to-onset <0.5 s; ≤4 unilateral leg movements, each 0.5–10 s long; ≤15 s total duration	Onset-to-onset <5 s
Respiratory-related leg movements	Included and then excluded from PLM series and/or reported separately	Excluded from PLMS series
Respiratory-related leg movements definition	Any leg movement occurring within ±0.5 s from the end of a respiratory event or from 2.0 s before to 10.25 s after the end of a respiratory event	Any leg movement occurring within 0.5 s before the start to 0.5 s after the end of an apnea or hypopnea, respiratory effort-related arousal, or sleep-disordered breathing event

PLM, periodic leg movements; PLMS, periodic leg movements during sleep; PLMW; periodic leg movements during resting wakefulness. [a]Leg movements lasting <0.5 s are disregarded; leg movements lasting >10 s stop the PLM series.

severe (scores 21–30) and very severe (scores 31–40)[119]. A validated and reliable self-administered version of the IRLS scale is also available[120]. In addition to the IRLS scale, clinicians should always weigh up the burden of RLS-related distress on social, occupational and educational domains and/or other areas of functioning like sleep, energy or vitality, daily activities, behaviour, cognition or mood.

Other diagnostic tests

A history of iron deficiency needs to be explored during clinical evaluation. Although usually unremarkable in idiopathic RLS, an accurate neurological examination is the last mandatory step of clinical evaluation. The presence of abnormal neurological signs suggests whether or not further diagnostic tests should be performed, in particular electromyography in the case of signs of neuropathy and neuroimaging in the case of signs of myelopathy.

No biological tests are strictly necessary for diagnosing RLS; however, a haematological screen, particularly at the first clinical evaluation, is recommended to identify secondary forms of RLS and manage the underlying disorder.

Haemoglobin, serum ferritin and transferrin saturation (percentage of iron binding) are the best easily available markers of iron deficiency. In inflammatory states, high levels of ferritin may not correspond to adequate iron storage and transferrin saturation needs to be evaluated. Although not easily accessible, owing to the invasive nature of the lumbar puncture, there is evidence of low levels of ferritin in CSF from patients with RLS who have normal sera ferritin levels[56,121]. Alternatively, brain iron content can be reliably evaluated via transcranial sonography of the substantia nigra, which is the main iron store in the brain[122]. As previously mentioned, hepcidin is under evaluation as a promising marker of RLS[59].

In patients with suspected renal insufficiency, creatinine levels should be measured, whereas rheumatological and inflammatory tests should be carried out in those with suspected rheumatic diseases. If neurological examination is suggestive of peripheral neuropathy, glycaemia and glycated haemoglobin, then folate and vitamin B_{12} or more specific tests might be considered.

PLM

PLM are very often associated with RLS. PLMS are recorded using polysomnography from each tibialis anterior muscle and often mimic the triple flexion reflex (dorsiflexion of the ankle and flexion of the knee and hip).

Two different sets of criteria are available for detecting and scoring PLMS from the American Academy of Sleep Medicine (AASM)[123] and the World Association of Sleep Medicine (WASM)[124] (TABLE 2). Here, we refer to the criteria from WASM because they are the most detailed.

PLM appear as leg movements with a duration between 0.5 and 10 s recorded on one leg (FIG. 3). The identification of PLM is carried out by marking all uninterrupted sequences of at least four candidate leg movements (unilateral or bilateral) separated by 10–90 s. Periods of >90 s without movements can interrupt the periodic sequence. After identification of periodic movements, the movements are classified as PLMS or PLMW. PLMS associated with arousals (overlapping or not separated by >0.5 s, disregarding which occurs first) are then counted, whereas those occurring around the end of respiratory events (see WASM criteria[124] for criteria) are classified as respiratory-related leg movements, not as PLMS. The most important parameter to take into account after the scoring of PLMS is their index (that is, number of movements per hours

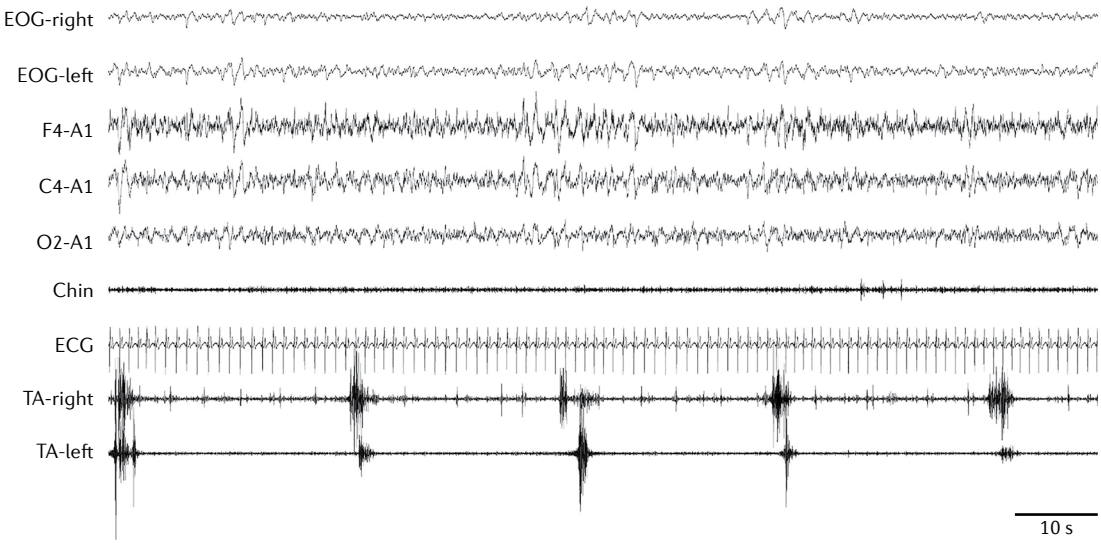

Fig. 3 | **Periodic leg movements during sleep.** Example of periodic leg movements during sleep (PLMS) in a patient with restless legs syndrome (RLS). Note that five bilateral movements are shown, occurring in a time window of 120 s.

of sleep), which is typically ≥15 in 70–80% of patients with RLS.

The diagnostic value of PLMS for RLS is low, owing to their low specificity for RLS[125]. PLMS also occur in many other sleep-related conditions, other diseases and in healthy individuals, particularly in the elderly. In the large-cohort polysomnography study HypnoLaus, comprising >2,000 individuals with a mean age of 51 years, a PLMS index >15 was found in 28% of participants[125]. Analysis of the degree of periodicity of PLMS (by means of graphs reporting their interval distribution or by calculating the so-called Periodicity Index) and observing a declining trend throughout the night also provides important information[126]. The use of the most recent WASM scoring criteria and the consideration of PLMS periodicity and time-of-night distribution can increase the specificity for RLS and identify a homogeneous motor pattern responding to dopaminergic agents and probably associated with specific genetic predisposing factors (such as *BTBD9*)[33].

In contrast to RLS, PLMS are more frequent in males than in females[125]. PLMS are often associated with cortical arousals and autonomic activation; however, their direct causal role in sleep disruption and their effect on the cardiovascular system is still under investigation[127]. PLMS can be associated with repeated increases in blood pressure and heart rate that lead to blunted nocturnal blood pressure dip and potentially resistant hypertension[128,129].

Paediatric RLS

Diagnostic criteria for paediatric RLS are the same as adult criteria[7]; however, in children, the description of symptoms must be in their own words. In this context, the applicability of diagnostic criteria to children is influenced by their language skills and cognitive development rather than age. Of note, infants, toddlers, or non-verbal children with RLS often present with bedtime irritability and delayed sleep onset[130]. A high awareness of the possibility of RLS in children by the clinician is needed to accurately identify and promptly treat these children.

Moreover, for paediatric RLS research, diagnostic criteria include 'probable' and 'possible' diagnosis of RLS. Probable RLS does not require the 'occurrence only or worsening in the evening or night'[7,131]. For possible RLS, behavioural manifestations of leg discomfort when sitting or lying must occur with movements of the affected limbs, and the discomfort must be worse at rest or during inactivity, relieved by movement, worsen in the evening or night, and must not be due solely to another medical or behavioural condition.

Family history of RLS in a first-degree relative and elevated PLMS on polysomnography (PLMS >5/hour) in the patient or elevated PLMS (>15/hour) in an adult first-degree relative are all factors supporting the diagnosis of paediatric RLS when the criteria are not clearly met. PLMS can often precede the diagnosis of RLS in young children[130]. Daytime consequences of paediatric RLS include impairment in the behavioural and educational domains[130]. As in adults, common mimics must be excluded; careful clinical assessment is often sufficient to exclude most of these mimics. However, assessing iron status is recommended in all children with RLS symptoms.

Management

In many cases, RLS is still incurable, so treatments focus on alleviating disease symptoms, which can be effectively managed if treatment is timely and adequate. However, RLS is often unrecognized or misdiagnosed. Consequently, patients with RLS often do not receive timely and appropriate treatment, which leads to the worsening of disease symptoms and unnecessary suffering. We may recommend first the assessment of systemic iron status and its appropriate treatment if needed, the management of comorbid sleep disorders and the assessment of the impact of medication that may aggravate or cause RLS. For infrequent and mild RLS, we recommend first non-pharmacological

strategies and occasional on-demand use of low-potency opioids (codeine or tramadol) or, rarely, carbidopa/levodopa. Few head-to-head studies comparing RLS treatments have been carried out, so clinicians often decide the order of therapies on the basis of the patient's comorbidities or potential adverse effects (FIG. 2). Of note, during pregnancy, most drugs that treat RLS (such as dopamine agonists and $\alpha_2\delta$ ligands) are contraindicated.

Non-pharmacological therapies

Non-pharmacological approaches for management of RLS may be adequate in patients with non-severe or infrequent intermittent RLS[132]. Regular physical exercise (conventional exercise and yoga), magnetic or electrical stimulation techniques, acupuncture, lifestyle interventions (pneumatic compression[133], light therapy and cognitive–behavioural therapy, especially in those with associated chronic insomnia and depressive symptoms), avoidance of exacerbating factors (such as iron deficiency and white wine), and sleep hygiene advice should always be considered initially[132].

Importantly, several medications can precipitate or exacerbate RLS symptoms. These medications include antihistamines, neuroleptics and other dopamine receptor antagonists, most antidepressants (although with less evidence for lithium)[134,135]. Discontinuation or dose adjustments of these medications should be considered in those with RLS, although it may be difficult to implement if they are needed for the management of comorbid disorders.

Pharmacotherapy

Iron therapy. Oral iron supplementation for 12 weeks should be considered for people with RLS who have low ferritin levels (<75 µg/l), and transferrin saturation <45%, although criteria to identify probable responders, and optimal formulations (often ferrous sulfate associated with vitamin C) and durations of treatment remain unclear[136]. Intravenous ferric carboxymaltose may also improve RLS symptoms in patients with moderate to severe RLS regardless of ferritin level[136]. An updated algorithm considered intravenous administration of ferric carboxymaltose if transferrin saturation was <45%, and one of the following: serum ferritin concentration <100 µg/l and a more rapid response than that with oral iron is desired; oral iron cannot be adequately absorbed owing to gastrointestinal disorders, bariatric surgery or chronic inflammatory conditions; oral iron is not tolerated; and RLS does not improve despite an adequate trial of oral intake of iron[134]. According to the consensus clinical practice guidelines, iron overload needs to be avoided[136].

Dopaminergic drugs. Dopamine agonists have been widely used for the management of RLS[137] and have remained the first-line therapy until recently. Many clinical trials have demonstrated the effectiveness of these drugs in alleviating RLS symptoms and PLMS. These medications target mainly D_3R, take approximately 1 hour to work, and, therefore, are suitable for use on demand[138].

Dopamine agonists used in the management of RLS include pramipexole, ropinirole and rotigotine. Pramipexole has level A evidence[139]. The most common adverse effects of pramipexole include orthostatic hypotension, headache, nausea and lower-limb oedema. Although infrequent, these classes of drugs can trigger compulsive and impulsive behaviours (see Quality of life, below) and should therefore be avoided in patients with a past history of such behaviours[140]. Also infrequent, but with potentially dangerous consequences in those who drive, daytime sleep attacks have also been observed with dopamine agonists, although mostly with treatment for Parkinson disease[141]. However, this effect is rare in RLS, as the daily dose of dopamine agonists is considerably lower than in patients with Parkinson disease. Ropinirole has an effectiveness and adverse effect profile that is very comparable to that of pramipexole[142]. Ropinirole was effective in improving RLS symptoms for up to 6 months according to two class I studies and up to 1 year according to two class I studies (level B evidence)[139]. Rotigotine (delivered through a transdermal patch allowing continuous release) reduced RLS symptoms for up to 6 months in two class I and three class II studies (level A evidence)[143], with results of sustained efficacy for patients with moderate-to-severe RLS at a stable dose for up to 5 years. Nevertheless, almost 50% of the patients needed to discontinue treatment owing to adverse effects, augmentation and lack of efficacy[143]. Owing to its unique route of delivery, rotigotine may be especially useful in patients with daytime symptoms, swallowing difficulties and those undergoing surgery. A small case study also showed that rotigotine improved PLM and RLS symptoms in the short term among patients with comorbid moderate to severe RLS and end-stage renal disease requiring haemodialysis[144]. In all patients with RLS, the dose of dopamine agonists should be kept as low as possible and the escalating dose should never exceed the maximum recommended dose.

Another two dopamine agonists, pergolide and cabergoline, are effective for RLS (level A evidence)[139]. However, all ergot-derived dopamine agonists are associated with severe adverse effects, including mediastinal fibrosis and valvulopathy, and therefore have been withdrawn from the market in most regions.

Over the past decade, the use of dopamine agonists for treatment of RLS has been reduced owing to the high incidence of 'augmentation' associated with long-term use of these drugs[145–147] (BOX 4). Augmentation remains a major problem with long-term daily use of levodopa in RLS, and affects 40–60% of patients after 8 years of follow-up. Among the dopamine agonists, drugs with the shortest half-life had the highest risk for augmentation, of up to 7% per year[148]. Rotigotine might have a lower risk of augmentation (in up to 4% of patients), although it remains controversial whether this is mainly due to a masking effect of its long half-life. The main strategy for preventing augmentation is to consider non-dopaminergic medications, such as $\alpha_2\delta$ ligands, for the initial treatment of RLS. Alternatively, daily doses of dopaminergic drugs should be kept as low as possible and never exceed maximum recommended doses[149]. Besides the initial efficacy of dopamine agonists on

sensory symptoms and PLM, the benefit of these medications on sleep might be less pronounced[149]. For patients with primary RLS in whom clinicians want to treat very severe RLS, high levels of PLMS, PLM and motor symptoms during the day, or comorbid psychiatric symptoms (such as depressive symptoms) dopaminergic agonists should be proposed first.

Levodopa was one of the first agents for RLS formally studied in clinical trials. Four class III studies that demonstrated a benefit of levodopa on RLS severity (level C evidence) have been reported[139]. Levodopa is recommended only for intermittent use in some regions for the treatment of RLS owing to the high risk of augmentation (BOX 4) and a possible intra-night rebound effect favoured by its short half-life[150].

$\alpha_2\delta$ ligands. Gabapentin, pregabalin and gabapentin enacarbil (a prodrug of gabapentin), also named the $\alpha_2\delta$ ligands, were initially approved as anticonvulsants and for neuropathic pain. However, these drugs also have superior efficacy for improving RLS and nighttime sleep compared with placebo and pramipexole[72]. A comparative study demonstrated that pregabalin was superior to two doses of pramipexole for improving RLS symptoms and sleep architecture over a 6-week period, with no improvement in PLM[72]. The only long-term comparative study compared pregabalin with two doses of pramipexole, and found an improvement in RLS symptoms over a 12-month treatment period with pregabalin and pramipexole, with the rate of RLS augmentation lower for pregabalin than for pramipexole[151]. Taken together, $\alpha_2\delta$ ligands are as effective over both the short term and the long term as dopamine agonists in the treatment of RLS dysesthesias, and $\alpha_2\delta$ ligands do not cause augmentation[72]. The rate of discontinuation owing to adverse effects (27% versus 24%) was similar for $\alpha_2\delta$ ligands and dopamine agonists and comprised somnolence, gait disturbance, dizziness, fatigue, weight gain and headache for $\alpha_2\delta$ ligands versus headache, nausea, nasopharyngitis and fatigue for dopamine agonists[124]. In addition, $\alpha_2\delta$ ligands may have a modest anxiolytic and sedative effect and may also help to control chronic pain. Accordingly, $\alpha_2\delta$ ligands are the preferred therapy in those with severe insomnia, comorbid pain, polyneuropathy, and generalized anxiety disorder associated with RLS.

Of note, it has been suggested that dopaminergic augmentation may reduce the response rate to future non-dopaminergic drugs, such as $\alpha_2\delta$ ligands[152]. As treatment with $\alpha_2\delta$ ligands seems to be safe and effective over the long term, the most recent guidelines for RLS recommend starting initial treatment of RLS with non-dopaminergic therapies, such as the $\alpha_2\delta$ ligands, in most cases[153].

Opioids. Opioids are considered a second-line or third-line treatment for RLS, and should be used either when symptoms are refractory to other treatments or owing to adverse effects of other treatments, such as augmentation, or in the case of associated severe pain disorder requiring drugs. Despite a consensus on the beneficial effects of low-dose opioids on RLS symptoms, few well-designed clinical trials have been carried out. Of note, low-dose methadone and oxycodone have demonstrated effectiveness for RLS[75,154], and extended-release oxycodone in combination with naloxone has been approved for refractory RLS in Europe[155]. Adverse effects include sedation, constipation, depression, anxiety and altered consciousness. Importantly, these drugs can also increase the risk for opioid-induced respiratory depression and substance use[154]. Opioids should be prescribed by a clinician who has received adequate training in treatment with these drugs. Close monitoring of patients receiving opioids is mandatory.

Box 4 | **Augmentation syndrome**

Augmentation is defined as a worsening of symptom severity manifesting as earlier onset of symptoms in the afternoon compared with before treatment initiation, a spread of symptoms to the upper arms, a shortening of the latency until onset of symptoms when at rest and an overall increase in symptom intensity. A paradoxical worsening of symptoms induced by an increase of the dose of dopamine agonists is another recognizable feature of augmentation.

Augmentation has been reported to occur with all dopaminergic drugs. The prevalence of augmentation is controversial, as it varies according to the drug, dose, half-life and duration of action, the duration and type of study, the criteria used to evaluate augmentation and the number of subjects[153]. Nevertheless, augmentation rates increase with the duration of studies; in short-term studies, rates of <10% have been reported[147,148,151,217,218], whereas rates are 30% in studies lasting 2–3 years, and 42–68% in studies lasting about 10 years[75,196].

Augmentation may be difficult to differentiate from RLS. As augmentation is progressive, it does not occur immediately after treatment initiation; however, the risk of augmentation increases with the duration and dose of treatment. Collectively, these features make it hard to prevent. The deterioration of RLS severity that occurs during augmentation may reduce the response rate to future non-dopaminergic therapies such as $\alpha_2\delta$ ligands[152]. The most recent guidelines aim to facilitate the identification of augmentation in patients with RLS by recommending that augmentation is considered in patients who have received stable treatment for ≥6 months and who request additional medication[153]. Four screening questions, relating to symptom onset, intensity and spread, and therapy dose and schedule, should be used routinely for this purpose in patients currently under treatment with dopaminergic agents[153].

Quality of life

In addition to many non-RLS specific QOL instruments, such as the SF-36, a RLS-specific questionnaire called the RLS-Quality of Life Instrument (RLS-QLI) is often used in clinical trials for RLS[156]. RLS has a remarkable contrast between non-visible symptoms and a strong effect on QOL. QOL scores in patients with RLS are influenced by symptom severity and frequency, and affect all domains of self-perceived health status[157]. Although patients with minimal or mild RLS symptoms have QOL scores similar to those of individuals without RLS, patients with RLS and severe symptoms report large decreases in the 'role physical', 'bodily pain', 'vitality' and 'general health' domains of the SF-36 (REFS[158,159]) (FIG. 4).

A major cause of the severe effect of RLS on QOL is the associated chronic sleep deprivation. Also, patients with RLS and comorbid disease report additional worsening of QOL compared with patients without RLS. Indeed, patients with chronic kidney disease undergoing haemodialysis with RLS had a poorer QOL than patients without RLS[160], and another study demonstrated that the treatment of RLS can improve their QOL[157]. In addition, RLS significantly worsens QOL in patients with myasthenia gravis[161] independently of disease duration and of

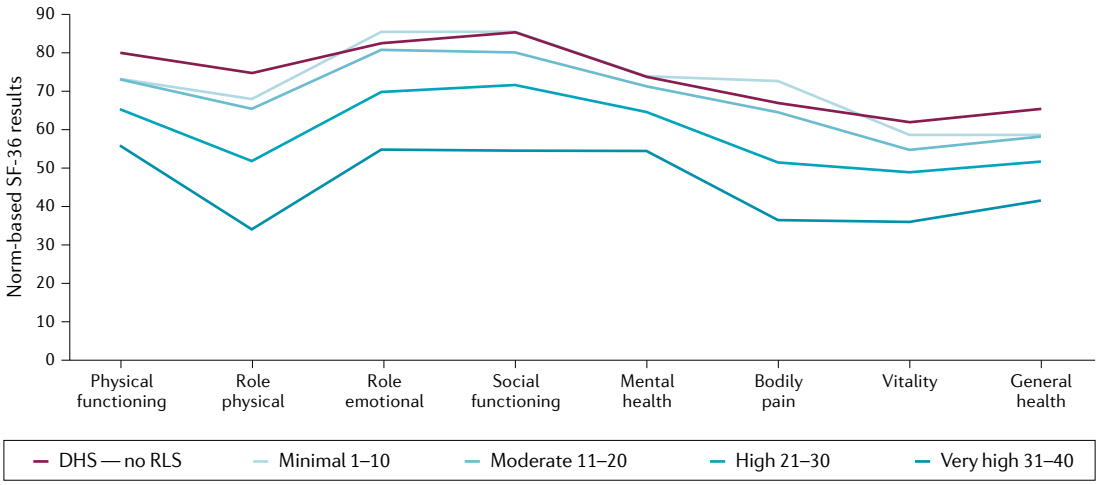

Fig. 4 | **Quality-of-life effects of RLS.** Quality-of-life domains (evaluated using SF-36 scores) according to the severity of restless legs syndrome (RLS) symptoms (determined using the IRLS scale) in the COR-Study and population controls. DHS, Dortmund Health Study; SF-36, 36-Item Short Form Survey. Data are from REF.[158] and REF.[159].

treatment of myasthenia gravis. Patients with multiple sclerosis and RLS also report poorer QOL, in addition to greater fatigue and anxiety levels compared with patients without comorbid RLS[162], similarly to patients with optic neuromyelitis[163]. Moreover, a lower QOL has been reported in patients with RLS and comorbid coronary artery disease[164], cancer[165], or neurodegenerative diseases such as Parkinson disease[166], and in whom a worsening of psychiatric problems and of their emotional and cognitive states has been reported, with a consequent negative effect on their QOL. Recent studies reported that severe RLS is a risk factor for suicide, suicidal thoughts and self-harm[3]. RLS occurring during pregnancy can be very severe, with a significant reduction of QOL owing to pain, leading to limitations in daily activities and decrease in performance[167].

Risk of hypertension and cardiovascular disorders

Cross-sectional and longitudinal studies have demonstrated the comorbidity of RLS with obesity, hypercholesterolaemia, diabetes mellitus, obstructive sleep apnoea, hypertension and other cardiovascular diseases[168–170]. Although large epidemiological studies have reported independent associations between RLS and cardiovascular diseases or hypertension[171], this relationship is controversial[172–176] and the underlying mechanisms are unclear. Mechanisms may include PLMS, sleep deprivation and iron deficiency; PLMS are often associated with micro-arousals that may contribute to sleep fragmentation and repeated increases in blood pressure and heart rate throughout the night[177–180]. The association between PLMS and high blood pressure in drug-free patients with RLS could increase the risk of blunted blood-pressure day-to-night dip, nocturnal hypertension and cardiovascular disease morbidity and mortality[181]. Indeed, one study found 24-hour blood-pressure deregulation with smaller declines in systolic blood pressure at night compared with daytime in patients with primary RLS[182]. In this study, hypertension was diagnosed in 11.9% of drug-free patients with RLS based on office measurements, and in 46.4% based on 24-hour blood-pressure monitoring, with night-time hypertension being twice as frequent as daytime hypertension. The loss of night-time blood pressure dip is one of the most sensitive predictors of cardiovascular disease morbidity and mortality[183]. One study assessed the effect of dopamine agonists on nocturnal blood-pressure elevations associated with PLMS, and found a significant reduction in systolic and diastolic blood-pressure elevations in rotigotine-treated patients compared with placebo[184]. Another monocentric double-blind placebo-controlled study showed that rotigotine increased the percentage of blood-pressure dipper profiles and the blood-pressure dip in patients with RLS, without any change in endothelial function[129]. Endothelial function alterations also predict cardiovascular disease morbidity but even controversial studies mostly reported normal endothelial function in drug-free RLS[185,186]. One population-based study confirmed the increased incidence of cardiovascular disease cases (myocardial infarction, angina, stroke, atrial fibrillation and heart failure) in RLS, with significantly lower cardiovascular disease risk in the group with effective treatment for RLS than in those without[187].

Risk of impulsive control disorders

Impulse control disorders (defined as pathological gambling, hypersexuality, compulsive shopping, eating and medication use) occur in patients with RLS with a prevalence of 5–17% in patients with RLS treated with dopamine agonists[140,188,189]. Dopamine agonists used for RLS treatment have high selective affinity for the D_2R and D_3R subtypes, which are expressed predominantly in the limbic areas of the brain, which are implicated in impulse control disorders. Impulse control disorders, impulsivity and substance addiction were infrequent (4–8%) in drug-free patients with RLS or in those treated with low doses of dopamine agonists[189,190]. By contrast, the prevalence of impulse control disorders is higher in patients with Parkinson disease, ranging from 2.6% to 34.8%, owing to different types and doses of dopaminergic drugs[191].

Patients with RLS (either drug-free or using dopamine agonists) have a preference towards risky choices on the Iowa Gambling Task (which assesses decision-making under ambiguity) and the Game of Dice Task (which assesses decision-making under risk); these risky choices are associated with negative long-term consequences[140,190]. These results allow the identification of individuals at risk of further development of impulse control disorders, which is a key finding because of their potentially devastating financial, social and marital consequences. Another study found that patients with RLS with augmentation have an almost sixfold increased risk of symptoms of impulse control disorders[192]. These data imply that augmentation and impulse control disorders may be related and may share a common pathophysiology.

Outlook

Education about RLS diagnosis and management is urgently needed to increase expertise of physicians of various subspecialities, including general practitioner, neurologists and sleep experts. It is equally important to intensify the search into the cause or causes of RLS and for new treatment strategies, to reduce suffering and substantial societal cost.

Understanding pathophysiology

The identification of genetic risk factors is extremely valuable for driving research into the pathophysiology of RLS. Thus, case–control genetic association studies with increased sample size and detection scope, in addition to whole-genome sequencing studies on well-characterized families with RLS, are needed to complete our knowledge of the genetic architecture of RLS. Further detailed functional studies are required to elucidate how sensorimotor circuits are involved in RLS, to detect the specific cell types affected and to identify the age at which pathophysiology starts, particularly in the context of change in MEIS1 activity. How the neurodevelopmental aspects of RLS relate to brain iron metabolism and the dopaminergic neurotransmission system also remains to be determined. RLS may be a prime case example for studying gene–environment interactions in model systems with a genetically susceptible brain structure that is confronted with additional factors based on clinical expertise, such as age, pregnancy, kidney dysfunction or iron deficiency. A reliable animal model of RLS would certainly help in achieving these goals. The identification of new clinical and polysomnographic phenotypes of RLS and biological markers, as well as the clarification of the relationship between RLS and PLMS, are further ambitious research goals.

Although improving our understanding of the aetiology of RLS is important, identifying and establishing personalized medicine for RLS will not be possible without further increasing our knowledge of the genetic basis of RLS. Such findings will be key for the development and application of genetic risk scores to stratify patients for therapies or prevention schemes[193,194].

Based on epidemiological associations between RLS, PLM, and hypertension and cardiovascular disorders, further studies should elucidate the underlying mechanisms of these associations, focusing on sleep but also on neural, metabolic, oxidative, inflammation and vascular assessment. Moreover, future clinical-based studies should also assess whether different treatments for RLS are associated with a reduction in long-term cardiovascular risk in RLS.

Novel therapeutic approaches

Lack of awareness and recognition of RLS among health-care professionals and general practitioners is the major cause of the inadequate care of patients with RLS[9]. Thus, policies and initiatives aiming to increase sleep education and related-disease recognition among medical students and doctors are important.

Although most studies demonstrate an initial improvement in symptoms, long-term studies and clinical experience reveal that treatment efficacy decreases with time, with risk of augmentation with dopaminergic drugs leading to treatment discontinuation and treatment failure. Thus the long-term consequences of dopaminergic drugs, and particularly dopaminergic augmentation[195], has led to the search of alternatives to these types of drug.

As previously mentioned, another type of drug that has shown therapeutic efficacy in RLS are the $\alpha_2\delta$ ligands. The mechanism of action of these agents is likely to be mediated by a reduction in the overall release of glutamate[71]. Thus, it is probable that other anti-glutamatergic drugs could also be effective for RLS. Indeed, one open-label study demonstrated an improvement in RLS symptoms, PLMS and sleep architecture following 8 weeks of treatment with perampanel (an AMPA receptor antagonist)[76]. Moreover, dipyridamole (which inhibits adenosine reuptake and regulates glutamatergic corticospinal terminals)[81,196] has also been shown to improve RLS symptoms, PLMS and sleep, demonstrated in an open-label study that has been replicated in a 2-week double-blind, placebo-controlled crossover study[84,85]. Of note, the degree of improvement of PLMS was similar to the one reported for dopamine agonists and was greater than the one observed for $\alpha_2\delta$ ligands[197]. In a single case, a beneficial effect of spinal cord stimulation in RLS has been reported[198–200], with one study showing promising effects of transcutaneous direct-current stimulation[201]. In addition, thalidomide was reported to be effective on RLS symptoms and sleep quality in an isolated patient with severe and resistant RLS[202]; however, this approach needs confirmation in larger studies. Genetic studies revealed associations with loci containing *CRBN* (encoding cereblon, the protein bound by thalidomide) and *MEIS2* (encoding cereblon's endogenous substrate, whose degradation is inhibited by the thalidomide–cereblon interaction)[40]. All these promising results need to be replicated in well-designed trials on a larger scale while looking carefully at the risk-to-benefit ratio.

Finally, evidence-based recommendations for long-term clinical management of RLS are needed. Several drugs are available to treat RLS; however, combination treatments that are commonly prescribed (low-dose dopaminergic drugs, α2δ ligands and opioids) should be rated as potentially more effective with fewer

safety concerns for long-term management of RLS. In addition, treatment of RLS in specific comorbid conditions is almost the same as treatment of primary RLS, although no (or only rare) studies have been conducted in concurrent RLS disorders[144]. Further clinical trials are needed to better evaluate the risk-to-benefit ratio of treating RLS associated with other conditions, to provide more personalized treatment options.

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1. Willis, T. *The London Practice of Physick* (Bassett & Cooke, 1685).
2. Ekbom, K. A. Restless legs: A clinical study. *Acta Med. Scand. Suppl*. **158**, 1–124 (1945).
3. Para, K. S. et al. Suicidal thought and behavior in individuals with restless legs syndrome. *Sleep. Med.* **54**, 1–7 (2019).
4. Whittom, S. et al. Age-at-onset in restless legs syndrome: a clinical and polysomnographic study. *Sleep. Med.* **9**, 54–59 (2007).
5. Rinaldi, F. et al. Defining the phenotype of restless legs syndrome/Willis–Ekbom disease (RLS/WED): a clinical and polysomnographic study. *J. Neurol.* **263**, 396–402 (2016).
6. Allen, R. P. & Earley, C. J. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. *Sleep. Med*. **1**, 11–19 (2000).
7. Allen, R. P. et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria — history, rationale, description, and significance. *Sleep. Med.* **15**, 860–873 (2014). **This consensus paper contains the most updated essential and supportive diagnostic criteria for RLS**.
8. Ondo, W. Restless Legs Syndrome 'Patient Odyssey' survey of disease burden on patient and spouses/partners. *Sleep. Med.* **47**, 51–53 (2018).
9. Trenkwalder, C. et al. Socioeconomic impact of restless legs syndrome and inadequate restless legs syndrome management across European settings. *Eur. J. Neurol.* **28**, 691–706 (2020).
10. Walters, A. S. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov. Disord.* **10**, 634–642 (1995).
11. Fulda, S. et al. We need to do better: a systematic review and meta-analysis of diagnostic test accuracy of restless legs syndrome screening instruments. *Sleep. Med. Rev.* **58**, 101461 (2021).
12. Picchietti, D. L., Van Den Eeden, S. K., Inoue, Y. & Berger, K. Achievements, challenges, and future perspectives of epidemiologic research in restless legs syndrome (RLS). *Sleep. Med.* **31**, 3–9 (2017).
13. Kim, T.-J. et al. Prevalence and characteristics of restless legs syndrome in Korean adults: a study in two independent samples of the general population. *Neuroepidemiology* **52**, 193–204 (2019).
14. Ma, J.-F. et al. Restless legs syndrome in Chinese elderly people of an urban suburb in Shanghai: a community-based survey. *Parkinsonism Relat. Disord.* **18**, 294–298 (2012).
15. Li, L.-H., Chen, H.-B., Zhang, L.-P., Wang, Z.-W. & Wang, C.-P. A community-based investigation on restless legs syndrome in a town in China. *Sleep. Med.* **13**, 342–345 (2012).
16. Berger, K. & Kurth, T. RLS epidemiology — frequencies, risk factors and methods in population studies. *Mov. Disord.* **22** (Suppl. 18), S420–S423 (2007).
17. Lee, H. B. et al. Race and restless legs syndrome symptoms in an adult community sample in east Baltimore. *Sleep. Med.* **7**, 642–645 (2006).
18. Szentkirályi, A. et al. Restless legs syndrome and all-cause mortality in four prospective cohort studies. *BMJ Open* **2**, e001652 (2012).
19. Kagimura, T., Nomura, T., Kusumi, M., Nakashima, K. & Inoue, Y. Prospective survey on the natural course of restless legs syndrome over two years in a closed cohort. *Sleep. Med.* **12**, 821–826 (2011).
20. Manconi, M. et al. When gender matters: restless legs syndrome. Report of the 'RLS and woman' workshop endorsed by the European RLS Study Group. *Sleep. Med. Rev.* **16**, 297–307 (2012).
21. Prosperetti, C. & Manconi, M. Restless legs syndrome/Willis–Ekbom disease and pregnancy. *Sleep. Med. Clin.* **10**, 323–329 (2015).
22. Manconi, M. et al. Restless legs syndrome and pregnancy. *Neurology* **63**, 1065–1069 (2004). **This study showed that pregnancy is a significant risk factor for RLS, finding a peak of incidence in the third trimester of pregnancy and a drop in frequency around delivery**.
23. Cesnik, E. et al. Transient RLS during pregnancy is a risk factor for the chronic idiopathic form. *Neurology* **75**, 2117–2120 (2010).
24. Zhang, J. et al. Restless legs symptoms in adolescents: epidemiology, heritability, and pubertal effects. *J. Psychosom. Res.* **76**, 158–164 (2014).
25. Szentkirályi, A., Völzke, H., Hoffmann, W., Trenkwalder, C. & Berger, K. Multimorbidity and the risk of restless legs syndrome in two prospective cohort studies. *Neurology* **82**, 2026–2033 (2014).
26. Trenkwalder, C., Allen, R., Högl, B., Paulus, W. & Winkelmann, J. Restless legs syndrome associated with major diseases: a systematic review and new concept. *Neurology* **86**, 1336–1343 (2016).
27. Batool-Anwar, S. et al. Lifestyle factors and risk of restless legs syndrome: prospective cohort study. *J. Clin. Sleep. Med.* **12**, 187–194 (2016).
28. Ondo, W. G., Vuong, K. D. & Wang, Q. Restless legs syndrome in monozygotic twins: clinical correlates. *Neurology* **55**, 1404–1406 (2000).
29. Allen, R. P., La Buda, M. C., Becker, P. & Earley, C. J. Family history study of the restless legs syndrome. *Sleep. Med.* **3** (Suppl.), S3–S7 (2002).
30. Ohayon, M. M., O'Hara, R. & Vitiello, M. V. Epidemiology of restless legs syndrome: a synthesis of the literature. *Sleep. Med. Rev.* **16**, 283–295 (2012).
31. Winkelmann, J. et al. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. *Ann. Neurol.* **52**, 297–302 (2002).
32. Ondo, W. & Jankovic, J. Restless legs syndrome: clinicoetiologic correlates. *Neurology* **47**, 1435–1441 (1996).
33. Stefansson, H. et al. A genetic risk factor for periodic limb movements in sleep. *N. Engl. J. Med.* **357**, 639–647 (2007).
34. Winkelmann, J. et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. *Nat. Genet.* **39**, 1000–1006 (2007).
35. Jiménez-Jiménez, F. J., Alonso-Navarro, H., García-Martín, E. & Agúndez, J. A. G. Genetics of restless legs syndrome: an update. *Sleep. Med. Rev.* **39**, 108–121 (2018).
36. Akçimen, F. et al. Screening of novel restless legs syndrome-associated genes in French-Canadian families. *Neurol. Genet.* **4**, e296 (2018).
37. Aridon, P. et al. A TRAPPC6B splicing variant associates to restless legs syndrome. *Parkinsonism Relat. Disord.* **31**, 135–138 (2016).
38. Gan-Or, Z. et al. Analysis of functional GLO1 variants in the BTBD9 locus and restless legs syndrome. *Sleep. Med.* **16**, 1151–1155 (2015).
39. Weissbach, A. et al. Exome sequencing in a family with restless legs syndrome. *Mov. Disord.* **27**, 1686–1689 (2012).
40. Schormair, B. et al. Identification of novel risk loci for restless legs syndrome in genome-wide association studies in individuals of European ancestry: a meta-analysis. *Lancet Neurol.* **16**, 898–907 (2017). **First large-scale (>15,000 cases in discovery stage) GWAS meta-analysis for RLS, which increased the number of risk loci from 6 to 19 and used pathway analyses for functional interpretation**.
41. Winkelmann, J. et al. Genome-wide association study identifies novel restless legs syndrome susceptibility loci on 2p14 and 16q12.1. *PLoS Genet.* **7**, e1002171 (2011).
42. Didriksen, M. et al. Large genome-wide association study identifies three novel risk variants for restless legs syndrome. *Commun. Biol.* **3**, 703 (2020). **Second large-scale (>10,000 cases in discovery stage) GWAS meta-analysis for RLS, which increased the number of identified risk loci and used Mendelian randomization analyses for functional interpretation**.
43. Akçimen, F. et al. Transcriptome-wide association study for restless legs syndrome identifies new susceptibility genes. *Commun. Biol.* **3**, 373 (2020).
44. Tilch, E. et al. Identification of restless legs syndrome genes by mutational load analysis. *Ann. Neurol.* **87**, 184–193 (2020).
45. Li, G. et al. Association of BTBD9 and MAP2K5/SKOR1 with restless legs syndrome in Chinese population. *Sleep* https://doi.org/10.1093/sleep/zsx028 (2017).
46. Sarayloo, F., Dion, P. A. & Rouleau, G. A. MEIS1 and restless legs syndrome: a comprehensive review. *Front. Neurol.* **10**, 935 (2019).
47. El Gewely, M. et al. Reassessing GWAS findings for the shared genetic basis of insomnia and restless legs syndrome. *Sleep* https://doi.org/10.1093/sleep/zsy164 (2018). **This is the only study dissecting the association of MEIS1 with insomnia symptoms and RLS using a sample of patients with chronic insomnia disorder, which had been phenotyped for both diseases by clinicians**.
48. Jansen, P. R. et al. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nat. Genet.* **51**, 394–403 (2019). **This is the largest GWAS meta-analysis on insomnia symptoms to date, which includes further attempts at dissecting the overlap between insomnia symptoms and RLS by means of GWAS**.
49. Hammerschlag, A. R. et al. Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. *Nat. Genet.* **49**, 1584–1592 (2017). **This meta-analysis was among the first studies to address the genetic overlap between RLS and insomnia symptoms based on GWAS results**.
50. Lane, J. M. et al. Biological and clinical insights from genetics of insomnia symptoms. *Nat. Genet.* **51**, 387–393 (2019).
51. Allen, R. P. & Earley, C. J. The role of iron in restless legs syndrome. *Mov. Disord.* **22** (Suppl. 18), S440–S448 (2007).
52. Allen, R. P., Auerbach, S., Bahrain, H., Auerbach, M. & Earley, C. J. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. *Am. J. Hematol.* **88**, 261–264 (2013).
53. Schmidauer, C. et al. Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome. *Ann. Neurol.* **58**, 630–634 (2005).
54. Godau, J., Schweitzer, K. J., Liepelt, I., Gerloff, C. & Berg, D. Substantia nigra hypoechogenicity: definition and findings in restless legs syndrome. *Mov. Disord.* **22**, 187–192 (2007).
55. Earley, C. J. et al. Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis–Ekbom disease). *Sleep. Med.* **15**, 1288–1301 (2014).
56. Earley, C. J. et al. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology* **54**, 1698–1700 (2000).
57. Connor, J. R. et al. Profile of altered brain iron acquisition in restless legs syndrome. *Brain J. Neurol.* **134**, 959–968 (2011).
58. Dauvilliers, Y. et al. Association between serum hepcidin level and restless legs syndrome. *Mov. Disord.* **33**, 618–627 (2018). **This is the first association between high hepcidin levels and RLS that emphasizes the complex peripheral iron metabolism deregulation in RLS**.
59. Chenini, S. et al. Hepcidin and ferritin levels in restless legs syndrome: a case-control study. *Sci. Rep.* **10**, 11914 (2020).
60. Earley, C. J., Uhl, G. R., Clemens, S. & Ferré, S. Connectome and molecular pharmacological differences in the dopaminergic system in restless legs syndrome (RLS): plastic changes and neuroadaptations that may contribute to augmentation. *Sleep. Med.* **31**, 71–77 (2017).
61. Dooley, D. J., Taylor, C. P., Donevan, S. & Feltner, D. Ca^{2+} channel $\alpha_2\delta$ ligands: novel modulators of neurotransmission. *Trends Pharmacol. Sci.* **28**, 75–82 (2007).
62. Connor, J. R. et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. *Brain J. Neurol.* **132**, 2403–2412 (2009).
63. Allen, R. P. Restless leg syndrome/Willis–Ekbom disease pathophysiology. *Sleep. Med. Clin.* **10**, 207–214 (2015).

64. Yepes, G. et al. Targeting hypersensitive corticostriatal terminals in restless legs syndrome. *Ann. Neurol.* **82**, 951–960 (2017).
This is the first article showing compelling evidence for an adenosinergic dysfunction in RLS.
65. Clemens, S., Rye, D. & Hochman, S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. *Neurology* **67**, 125–130 (2006).
This seminal theoretical paper suggested the involvement of the dopaminergic inhibitory hypthalamo-spinal pathway in the pathogenesis of RLS.
66. Qu, S. et al. Locomotion is increased in A11-lesioned mice with iron deprivation: a possible animal model for restless legs syndrome. *J. Neuropathol. Exp. Neurol.* **66**, 383–388 (2007).
67. Earley, C. J., Allen, R. P., Connor, J. R., Ferrucci, L. & Troncoso, J. The dopaminergic neurons of the A11 system in RLS autopsy brains appear normal. *Sleep. Med.* **10**, 1155–1157 (2009).
68. Unger, E. L., Bianco, L. E., Jones, B. C., Allen, R. P. & Earley, C. J. Low brain iron effects and reversibility on striatal dopamine dynamics. *Exp. Neurol.* **261**, 462–468 (2014).
69. Oertel, W. H. et al. Rotigotine transdermal patch in moderate to severe idiopathic restless legs syndrome: a randomized, placebo-controlled polysomnographic study. *Sleep. Med.* **11**, 848–856 (2010).
70. Altarifi, A. A. et al. Effects of acute and repeated treatment with the biased μ-opioid receptor agonist TRV130 (oliceridine) on measures of antinociception, gastrointestinal function, and abuse liability in rodents. *J. Psychopharmacol. Oxf. Engl.* **31**, 730–739 (2017).
71. Allen, R. P., Barker, P. B., Horská, A. & Earley, C. J. Thalamic glutamate/glutamine in restless legs syndrome: increased and related to disturbed sleep. *Neurology* **80**, 2028–2034 (2013).
This was the first study suggesting a disturbance of glutamatergic transmission in RLS, and suggesting the mechanisms of action of glutamatergic drugs (that is, $\alpha_2\delta$ ligands) and other arousal-reducing agents.
72. Garcia-Borreguero, D. et al. Pregabalin versus pramipexole: effects on sleep disturbance in restless legs syndrome. *Sleep* **37**, 635–643 (2014).
73. Kapur, N. & Friedman, R. Oral ketamine: a promising treatment for restless legs syndrome. *Anesth. Analg.* **94**, 1558–1559 (2002).
74. Inturrisi, C. E. Pharmacology of methadone and its isomers. *Minerva Anestesiol.* **71**, 435–437 (2005).
75. Silver, N., Allen, R. P., Senerth, J. & Earley, C. J. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. *Sleep. Med.* **12**, 440–444 (2011).
76. Garcia-Borreguero, D., Cano, I. & Granizo, J. J. Treatment of restless legs syndrome with the selective AMPA receptor antagonist perampanel. *Sleep. Med.* **34**, 105–108 (2017).
77. Inoue, Y. et al. Efficacy and safety of pramipexole in Japanese patients with primary restless legs syndrome: a polysomnographic randomized, double-blind, placebo-controlled study. *Sleep. Med.* **11**, 11–16 (2010).
78. Shukla, A., Agarwal, K. N. & Shukla, G. S. Latent iron deficiency alters γ-aminobutyric acid and glutamate metabolism in rat brain. *Experientia* **45**, 343–345 (1989).
79. McGahan, M. C. et al. Iron alters glutamate secretion by regulating cytosolic aconitase activity. *Am. J. Physiol. Cell Physiol.* **288**, C1117–C1124 (2005).
80. Quiroz, C. et al. Adenosine receptors as markers of brain iron deficiency: implications for restless legs syndrome. *Neuropharmacology* **111**, 160–168 (2016).
81. Ferré, S. et al. Pivotal role of adenosine neurotransmission in restless legs syndrome. *Front. Neurosci.* **11**, 722 (2017).
82. Ciruela, F. et al. Heterodimeric adenosine receptors: a device to regulate neurotransmitter release. *Cell. Mol. Life Sci.* **63**, 2427–2431 (2006).
83. Ferré, S. et al. Essential control of the function of the striatopallidal neuron by pre-coupled complexes of adenosine A2A-dopamine D2 receptor heterotetramers and adenylyl cyclase. *Front. Pharmacol.* **9**, 243 (2018).
84. Garcia-Borreguero, D. et al. Treatment of restless legs syndrome/Willis–Ekbom disease with the non-selective ENT1/ENT2 inhibitor dipyridamole: testing the adenosine hypothesis. *Sleep. Med.* **45**, 94–97 (2018).
85. Garcia-Borreguero, D., Garcia-Malo, C., Granizo, J. J. & Ferré, S. A randomized, placebo-controlled crossover study with dipyridamole for restless legs syndrome. *Mov. Disord.* https://doi.org/10.1002/mds.28668 (2021).
Main clinical evidence showing the involvement of adenosinergic mechanisms in the pathophysiology of RLS and the therapeutic effects of dipyridamole in RLS.
86. Magalhães, S. C. et al. Transcranial magnetic stimulation for evaluation of motor cortical excitability in restless legs syndrome/Willis–Ekbom disease. *Sleep. Med.* **16**, 1265–1273 (2015).
87. Lanza, G. et al. Impaired short-term plasticity in restless legs syndrome: a pilot rTMS study. *Sleep. Med.* **46**, 1–4 (2018).
88. Lanza, G. & Ferri, R. The neurophysiology of hyperarousal in restless legs syndrome: hints for a role of glutamate/GABA. *Adv. Pharmacol. San. Diego Calif.* **84**, 101–119 (2019).
This paper summarizes the neurophysiological and biological basis of hyperarousal in RLS.
89. Provini, F. et al. Motor pattern of periodic limb movements during sleep. *Neurology* **57**, 300–304 (2001).
90. Ferri, R. et al. Acute dopamine-agonist treatment in restless legs syndrome: effects on sleep architecture and NREM sleep instability. *Sleep* **33**, 793–800 (2010).
91. Lanza, G. et al. Central and peripheral nervous system excitability in restless legs syndrome. *Sleep. Med.* **31**, 49–60 (2017).
92. Walters, A. S. et al. Restless legs syndrome shows increased silent postmortem cerebral microvascular disease with gliosis. *J. Am. Heart Assoc.* **10**, e019627 (2021).
93. de Paiva, J. P. Q. et al. Sensorimotor white matter projections and disease severity in primary restless legs syndrome/Willis–Ekbom disease: a multimodal DTI analysis. *Sleep. Med.* **73**, 106–116 (2020).
94. Kocar, T. D., Müller, H.-P. & Kassubek, J. Differential functional connectivity in thalamic and dopaminergic pathways in restless legs syndrome: a meta-analysis. *Ther. Adv. Neurol. Disord.* **13**, 1756286420941670 (2020).
95. Stefani, A. et al. Multimodal magnetic resonance imaging reveals alterations of sensorimotor circuits in restless legs syndrome. *Sleep* **42**, zsz171 (2019).
96. Tuovinen, N. et al. Functional connectivity and topology in patients with restless legs syndrome: a case-control resting-state functional magnetic resonance imaging study. *Eur. J. Neurol.* **28**, 448–458 (2021).
97. Gupta, R., Ulfberg, J., Allen, R. P. & Goel, D. High prevalence of restless legs syndrome/Willis Ekbom Disease (RLS/WED) among people living at high altitude in the Indian Himalaya. *Sleep. Med.* **35**, 7–11 (2017).
98. Castillo, P. R., Kaplan, J., Lin, S.-C., Fredrickson, P. A. & Mahowald, M. W. Prevalence of restless legs syndrome among native South Americans residing in coastal and mountainous areas. *Mayo Clin. Proc.* **81**, 1345–1347 (2006).
99. Stefani, A., Heidbreder, A., Hackner, H., Burtscher, M. & Högl, B. Influence of high altitude on periodic leg movements during sleep in individuals with restless legs syndrome and healthy controls: a pilot study. *Sleep. Med.* **29**, 88–89 (2017).
100. Sevim, S. et al. Unexpectedly low prevalence and unusual characteristics of RLS in Mersin, Turkey. *Neurology* **61**, 1562–1569 (2003).
101. Sun, S. et al. Association between leg motor restlessness and depression among Chinese males living at high-altitude: the mediating role of insomnia. *Sleep. Breath. Schlaf Atm.* **25**, 979–987 (2021).
102. Budhiraja, R., Siddiqi, T. A. & Quan, S. F. Sleep disorders in chronic obstructive pulmonary disease: etiology, impact, and management. *J. Clin. Sleep. Med.* **11**, 259–270 (2015).
103. Salminen, A. V., Rimpilä, V. & Polo, O. Peripheral hypoxia in restless legs syndrome (Willis–Ekbom disease). *Neurology* **82**, 1856–1861 (2014).
This study showed a correlation of peripheral hypoxia with the appearance and severity of RLS symptoms, which was reversed by dopamine agonist.
104. Okamura, T., Yamazaki, M. & Toda, N. Responses to dopamine of isolated human and monkey veins compared with those of the arteries. *J. Pharmacol. Exp. Ther.* **258**, 275–279 (1991).
105. Larsson, B. W., Kadi, F., Ulfberg, J. & Aulin, K. P. Skeletal muscle morphology in patients with restless legs syndrome. *Eur. Neurol.* **58**, 133–137 (2007).
106. Wåhlin-Larsson, B., Ulfberg, J., Aulin, K. P. & Kadi, F. The expression of vascular endothelial growth factor in skeletal muscle of patients with sleep disorders. *Muscle Nerve* **40**, 556–561 (2009).
107. Yeh, W.-L., Lu, D.-Y., Lin, C.-J., Liou, H.-C. & Fu, W.-M. Inhibition of hypoxia-induced increase of blood-brain barrier permeability by YC-1 through the antagonism of HIF-1α accumulation and VEGF expression. *Mol. Pharmacol.* **72**, 440–449 (2007).
108. Michaud, M., Chabli, A., Lavigne, G. & Montplaisir, J. Arm restlessness in patients with restless legs syndrome. *Mov. Disord.* **15**, 289–293 (2000).
109. Winkelmann, J. et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. *Sleep* **23**, 597–602 (2000).
110. Bassetti, C. L., Mauerhofer, D., Gugger, M., Mathis, J. & Hess, C. W. Restless legs syndrome: a clinical study of 55 patients. *Eur. Neurol.* **45**, 67–74 (2001).
111. Hening, W. A. et al. Circadian rhythm of motor restlessness and sensory symptoms in the idiopathic restless legs syndrome. *Sleep* **22**, 901–912 (1999).
112. Michaud, M. et al. Circadian rhythm of restless legs syndrome: relationship with biological markers. *Ann. Neurol.* **55**, 372–380 (2004).
113. Trenkwalder, C. et al. Circadian rhythm of periodic limb movements and sensory symptoms of restless legs syndrome. *Mov. Disord.* **14**, 102–110 (1999).
114. Montplaisir, J. et al. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov. Disord.* **12**, 61–65 (1997).
115. Ulfberg, J. et al. Comorbidity in restless legs syndrome among a sample of Swedish adults. *Sleep. Med.* **8**, 768–772 (2007).
116. Allen, R. P., Stillman, P. & Myers, A. J. Physician-diagnosed restless legs syndrome in a large sample of primary medical care patients in western Europe: prevalence and characteristics. *Sleep. Med.* **11**, 31–37 (2010).
117. Garcia-Borreguero, D. et al. The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep. Med.* **14**, 675–684 (2013).
118. Gamaldo, C., Benbrook, A. R., Allen, R. P., Oguntimein, O. & Earley, C. J. Evaluating daytime alertness in individuals with restless legs syndrome (RLS) compared to sleep restricted controls. *Sleep. Med.* **10**, 134–138 (2009).
119. Walters, A. S. et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep. Med.* **4**, 121–132 (2003).
This study validated the scale most often used to quantify and monitor RLS severity.
120. Sharon, D. et al. Validation of the self-administered version of the International Restless Legs Syndrome Study Group severity rating scale — the sIRLS. *Sleep. Med.* **54**, 94–100 (2019).
121. Mizuno, S., Mihara, T., Miyaoka, T., Inagaki, T. & Horiguchi, J. CSF iron, ferritin and transferrin levels in restless legs syndrome. *J. Sleep. Res.* **14**, 43–47 (2005).
122. Garcia-Malo, C. et al. Quantitative transcranial sonography of the substantia nigra as a predictor of therapeutic response to intravenous iron therapy in restless legs syndrome. *Sleep. Med.* **66**, 123–129 (2020).
123. Iber, C. et al. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications* (American Academy of Sleep Medicine, 2021).
124. Ferri, R. et al. World Association of Sleep Medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms developed by a joint task force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG). *Sleep. Med.* **26**, 86–95 (2016).
These are the most recent, updated and data-driven scoring criteria for PLMS.
125. Haba-Rubio, J. et al. Clinical significance of periodic limb movements during sleep: the HypnoLaus study. *Sleep. Med.* **41**, 45–50 (2018).
This is one of the largest cohort studies on PLMS in the general population.
126. Ferri, R. et al. Computer-assisted detection of nocturnal leg motor activity in patients with restless legs syndrome and periodic leg movements during sleep. *Sleep* **28**, 998–1004 (2005).

127. Manconi, M. et al. Dissociation of periodic leg movements from arousals in restless legs syndrome. *Ann. Neurol.* **71**, 834–844 (2012).
128. Hein, M., Lanquart, J.-P., Hubain, P. & Loas, G. Risk of resistant hypertension associated with restless legs syndrome and periodic limb movements during sleep: a study on 673 treated hypertensive individuals. *Sleep. Med.* **63**, 46–56 (2019).
129. Chenini, S. et al. Increased blood pressure dipping in restless legs syndrome with rotigotine: a randomized trial. *Mov. Disord.* **35**, 2164–2173 (2020).
This was the first study showing that rotigotine increased the percentage of blood pressure dipper profiles in patients with RLS.
130. Durmer, J. S. & Quraishi, G. H. Restless legs syndrome, periodic leg movements, and periodic limb movement disorder in children. *Pediatr. Clin. North Am.* **58**, 591–620 (2011).
131. Picchietti, D. L. et al. Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. *Sleep. Med.* **14**, 1253–1259 (2013).
This paper reports specific diagnostic criteria for pediatric RLS.
132. Bega, D. & Malkani, R. Alternative treatment of restless legs syndrome: an overview of the evidence for mind-body interventions, lifestyle interventions, and neutraceuticals. *Sleep. Med.* **17**, 99–105 (2016).
133. Lettieri, C. J. & Eliasson, A. H. Pneumatic compression devices are an effective therapy for restless legs syndrome: a prospective, randomized, double-blinded, sham-controlled trial. *Chest* **135**, 74–80 (2009).
134. Silber, M. H. et al. The management of restless legs syndrome: an updated algorithm. *Mayo Clin. Proc.* **96**, 1921–1937 (2021).
135. Patatanian, E. & Claborn, M. K. Drug-induced restless legs syndrome. *Ann. Pharmacother.* **52**, 662–672 (2018).
136. Allen, R. P. et al. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis–Ekbom disease in adults and children: an IRLSSG task force report. *Sleep. Med.* **41**, 27–44 (2018).
These consensus guidelines provided indication and instructions to supplement with oral or intravenous iron patients with RLS.
137. Akpinar, S. Treatment of restless legs syndrome with levodopa plus benserazide. *Arch. Neurol.* **39**, 739 (1982).
138. Manconi, M. et al. Preferential D2 or preferential D3 dopamine agonists in restless legs syndrome. *Neurology* **77**, 110–117 (2011).
139. Winkelman, J. W. et al. Practice guideline summary: treatment of restless legs syndrome in adults: report of the guideline development, dissemination, and implementation subcommittee of the american academy of neurology. *Neurology* **87**, 2585–2593 (2016).
140. Bayard, S., Langenier, M. C. & Dauvilliers, Y. Decision-making, reward-seeking behaviors and dopamine agonist therapy in restless legs syndrome. *Sleep* **36**, 1501–1507 (2013).
141. Möller, J. C. et al. "Sleep attacks" in Parkinson patients. A side effect of nonergoline dopamine agonists or a class effect of dopamine agonists? *Nervenarzt* **71**, 670–676 (2000).
142. Zintzaras, E. et al. Randomized trials of dopamine agonists in restless legs syndrome: a systematic review, quality assessment, and meta-analysis. *Clin. Ther.* **32**, 221–237 (2010).
143. Oertel, W. et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. *Lancet Neurol.* **10**, 710–720 (2011).
144. Dauvilliers, Y. et al. Rotigotine in hemodialysis-associated restless legs syndrome: a randomized controlled trial. *Am. J. Kidney Dis.* **68**, 434–443 (2016).
145. Lipford, M. C. & Silber, M. H. Long-term use of pramipexole in the management of restless legs syndrome. *Sleep. Med.* **13**, 1280–1285 (2012).
146. Mitterling, T. et al. Natural course of restless legs syndrome/Willis–Ekbom disease: long-term observation of a large clinical cohort. *Sleep. Med.* **16**, 1252–1258 (2015).
This is the main long-term therapeutic comparison between a dopamine agonist and an $\alpha_2\delta$ ligand.
147. Allen, R. P. et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. *Sleep. Med.* **12**, 431–439 (2011).
This article shows the prevalence of dopaminergic augmentation in the USA, and how few of these cases are identified by their physicians.
148. Högl, B. et al. Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome. *Sleep. Med.* **12**, 351–360 (2011).
149. Garcia-Borreguero, D., Cano-Pumarega, I. & Marulanda, R. Management of treatment failure in restless legs syndrome (Willis–Ekbom disease). *Sleep. Med. Rev.* **41**, 50–60 (2018).
150. Allen, R. P. & Earley, C. J. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep* **19**, 205–213 (1996).
This is the first study describing the phenomenon of augmentation in a sample of patients with RLS treated with carbidopa/levodopa.
151. Allen, R. P. et al. Comparison of pregabalin with pramipexole for restless legs syndrome. *N. Engl. J. Med.* **370**, 621–631 (2014).
152. Wanner, V., Garcia Malo, C., Romero, S., Cano-Pumarega, I. & Garcia-Borreguero, D. Non-dopaminergic vs. dopaminergic treatment options in restless legs syndrome. *Adv. Pharmacol. San. Diego Calif.* **84**, 187–205 (2019).
153. Garcia-Borreguero, D. et al. Guidelines for the first-line treatment of restless legs syndrome/Willis–Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. *Sleep. Med.* **21**, 1–11 (2016).
This is the most recent algorithm on how to prevent and treat augmentation.
154. Silber, M. H. et al. The appropriate use of opioids in the treatment of refractory restless legs syndrome. *Mayo Clin. Proc.* **93**, 59–67 (2018).
155. Trenkwalder, C. et al. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. *Lancet Neurol.* **12**, 1141–1150 (2013).
156. Atkinson, M. J. et al. Validation of the restless legs syndrome quality of life instrument (RLS-QLI): findings of a consortium of national experts and the RLS Foundation. *Qual. Life Res.* **13**, 679–693 (2004).
157. Giannaki, C. D. et al. Restless legs syndrome is contributing to fatigue and low quality of life levels in hemodialysis patients. *World J. Nephrol.* **6**, 236–242 (2017).
158. Fuhs, A. et al. Effects of short- and long-term variations in RLS severity on perceived health status — the COR-study. *PLoS ONE* **9**, e94821 (2014).
159. Szentkiralyi, A., Fendrich, K., Hoffmann, W., Happe, S. & Berger, K. Incidence of restless legs syndrome in two population-based cohort studies in Germany. *Sleep. Med.* **12**, 815–820 (2011).
160. Kutlu, R., Selcuk, N. Y., Sayin, S. & Kal, O. Restless legs syndrome and quality of life in chronic hemodialysis patients. *Niger. J. Clin. Pract.* **21**, 573–577 (2018).
161. Ataide, M. F., da Cunha-Correia, C. & Petribú, K. C. L. The relationship between restless legs syndrome and quality of life in patients with myasthenia gravis. *Eur. Neurol.* **81**, 205–208 (2019).
162. Cederberg, K. L. J. et al. Restless legs syndrome and health-related quality of life in adults with multiple sclerosis. *J. Sleep. Res.* **29**, e12880 (2020).
163. Barzegar, M. et al. Comparison of sleep complaints and quality of life between patients with neuromyelitis optica spectrum disorder (NMOSD) and healthy controls. *Mult. Scler. Relat. Disord.* **32**, 81–87 (2019).
164. Yatsu, S. et al. Prevalence and significance of restless legs syndrome in patients with coronary artery disease. *Am. J. Cardiol.* **123**, 1580–1586 (2019).
165. Ostacoli, L. et al. Restless legs syndrome and its relationship with anxiety, depression, and quality of life in cancer patients undergoing chemotherapy. *Qual. Life Res.* **19**, 531–537 (2010).
166. Fereshtehnejad, S.-M., Shafieesabet, M., Shahidi, G. A., Delbari, A. & Lökk, J. Restless legs syndrome in patients with Parkinson's disease: a comparative study on prevalence, clinical characteristics, quality of life and nutritional status. *Acta Neurol. Scand.* **131**, 211–218 (2015).
167. Akbaş, P. & Sözbir, Ş. Y. Restless legs syndrome and quality of life in pregnant women. *Rev. Assoc. Med. Bras.* **65**, 618–624 (2019).
168. De Vito, K. et al. Prospective study of obesity, hypertension, high cholesterol, and risk of restless legs syndrome. *Mov. Disord.* **29**, 1044–1052 (2014).
169. Gao, X., Schwarzschild, M. A., Wang, H. & Ascherio, A. Obesity and restless legs syndrome in men and women. *Neurology* **72**, 1255–1261 (2009).
170. Schlesinger, I., Erikh, I., Avizohar, O., Sprecher, E. & Yarnitsky, D. Cardiovascular risk factors in restless legs syndrome. *Mov. Disord.* **24**, 1587–1592 (2009).
171. Gottlieb, D. J., Somers, V. K., Punjabi, N. M. & Winkelman, J. W. Restless legs syndrome and cardiovascular disease: a research roadmap: a response. *Sleep. Med.* **36**, 181 (2017).
172. Winkelman, J. W., Shahar, E., Sharief, I. & Gottlieb, D. J. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. *Neurology* **70**, 35–42 (2008).
173. Batool-Anwar, S. et al. Restless legs syndrome and hypertension in middle-aged women. *Hypertension* **58**, 791–796 (2011).
174. Winter, A. C. et al. Restless legs syndrome and risk of incident cardiovascular disease in women and men: prospective cohort study. *BMJ Open* **2**, e000866 (2012).
175. Pepin, J.-L. et al. Hypertension and sleep: overview of a tight relationship. *Sleep. Med. Rev.* **18**, 509–519 (2014).
176. Cholley-Roulleau, M. et al. Restless legs syndrome and cardiovascular diseases: a case-control study. *PLoS ONE* **12**, e0176552 (2017).
177. Pennestri, M.-H. et al. Blood pressure changes associated with periodic leg movements during sleep in healthy subjects. *Sleep. Med.* **14**, 555–561 (2013).
This is the first study that demonstrated and quantified the association of RLS-related PLMS with phasic significant increases in blood pressure.
178. Cassel, W. et al. Significant association between systolic and diastolic blood pressure elevations and periodic limb movements in patients with idiopathic restless legs syndrome. *Sleep. Med.* **17**, 109–120 (2016).
179. Winkelman, J. W. The evoked heart rate response to periodic leg movements of sleep. *Sleep* **22**, 575–580 (1999).
180. Wing, Y. K., Zhang, J., Ho, C. K. W., Au, C.-T. & Li, A. M. Periodic limb movement during sleep is associated with nocturnal hypertension in children. *Sleep* **33**, 759–765 (2010).
181. Hermida, R. C., Ayala, D. E., Mojón, A. & Fernández, J. R. Blunted sleep-time relative blood pressure decline increases cardiovascular risk independent of blood pressure level — the 'normotensive non-dipper' paradox. *Chronobiol. Int.* **30**, 87–98 (2013).
182. Chenini, S. et al. Blood pressure profile and endothelial function in restless legs syndrome. *Sci. Rep.* **9**, 15933 (2019).
183. Boggia, J. et al. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet* **370**, 1219–1229 (2007).
184. Bauer, A. et al. Rotigotine's effect on PLM-associated blood pressure elevations in restless legs syndrome: an RCT. *Neurology* **86**, 1785–1793 (2016).
This was the first study to provide class I evidence that for patients with RLS, rotigotine reduced PLM-associated nocturnal systolic blood pressure elevations.
185. Rubinshtein, R. et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur. Heart J.* **31**, 1142–1148 (2010).
186. Koh, S. Y., Kim, M. S., Lee, S. M., Hong, J. M. & Yoon, J. H. Impaired vascular endothelial function in patients with restless legs syndrome: a new aspect of the vascular pathophysiology. *J. Neurol. Sci.* **359**, 207–210 (2015).
187. Gao, X. et al. Treating restless legs syndrome was associated with low risk of cardiovascular disease: a cohort study with 3.4 years of follow-up. *J. Am. Heart Assoc.* **10**, e018674 (2021).
188. Tippmann-Peikert, M., Park, J. G., Boeve, B. F., Shepard, J. W. & Silber, M. H. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. *Neurology* **68**, 301–303 (2007).
189. Cornelius, J. R., Tippmann-Peikert, M., Slocumb, N. L., Frerichs, C. F. & Silber, M. H. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. *Sleep* **33**, 81–87 (2010).
190. Bayard, S., Yu, H., Langenier, M. C., Carlander, B. & Dauvilliers, Y. Decision making in restless legs syndrome. *Mov. Disord.* **25**, 2634–2640 (2010).

191. Grall-Bronnec, M. et al. Dopamine agonists and impulse control disorders: a complex association. *Drug Saf.* **41**, 19–75 (2018).
192. Heim, B. et al. Augmentation and impulsive behaviors in restless legs syndrome: coexistence or association? *Neurology* **87**, 36–40 (2016).
193. Mars, N. et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. *Nat. Med.* **26**, 549–557 (2020).
194. Kapoor, P. M. et al. Combined associations of a polygenic risk score and classical risk factors with breast cancer risk. *J. Natl Cancer Inst.* **113**, 329–337 (2020).
195. García-Borreguero, D. Dopaminergic augmentation in restless legs syndrome/Willis–Ekbom disease: identification and management. *Sleep. Med. Clin.* **10**, 287–292 (2015).
196. Garcia-Borreguero, D. et al. Reduced response to gabapentin enacarbil in restless legs syndrome following long-term dopaminergic treatment. *Sleep. Med.* **55**, 74–80 (2019).
197. Fulda, S. & Wetter, T. C. Where dopamine meets opioids: a meta-analysis of the placebo effect in restless legs syndrome treatment studies. *Brain J. Neurol.* **131**, 902–917 (2008).
198. Adil, S. M., Han, J. L., Parente, B. A., Hickey, P. & Lad, S. P. Spinal cord stimulation for restless legs syndrome: case series and mechanistic hypothesis. *Stereotact. Funct. Neurosurg.* **97**, 31–36 (2019).
199. De Vloo, P. et al. Successful spinal cord stimulation for severe medication-refractory restless legs syndrome. *Mov. Disord.* **34**, 585–586 (2019).
200. Byrne, D. A., Sobey, C. M., Trahan, J., Bagai, K. & Walters, A. Spinal cord stimulation in patients with chronic pain and restless legs syndrome: a case report. *AA Pract.* **13**, 110–113 (2019).
201. Heide, A. C. et al. Effects of transcutaneous spinal direct current stimulation in idiopathic restless legs patients. *Brain Stimul.* **7**, 636–642 (2014).
202. Salminen, A. V., Schandra, N., Schormair, B., Oexle, K. & Winkelmann, J. Therapeutic effectiveness of thalidomide in a patient with treatment-resistant restless legs syndrome. *J. Clin. Sleep. Med.* **16**, 1815–1817 (2020).
203. Kwatra, V. et al. Differential diagnosis and treatment of restless legs syndrome: a literature review. *Cureus* **10**, e3297 (2018).
204. Salminen, A. V., Lam, D. D. & Winkelmann, J. Role of MEIS1 in restless legs syndrome: from GWAS to functional studies in mice. *Adv. Pharmacol. San. Diego Calif.* **84**, 175–184 (2019).
205. Bouilloux, F. et al. Loss of the transcription factor Meis1 prevents sympathetic neurons target-field innervation and increases susceptibility to sudden cardiac death. *eLife* **5**, e11627 (2016).
206. Owa, T. et al. Meis1 coordinates cerebellar granule cell development by regulating Pax6 transcription, BMP signaling and ATOH1 degradation. *J. Neurosci.* **38**, 1277–1294 (2018).
207. Rataj-Baniowska, M. et al. Retinoic acid receptor β controls development of striatonigral projection neurons through FGF-dependent and Meis1-dependent mechanisms. *J. Neurosci.* **35**, 14467–14475 (2015).
208. Spieler, D. et al. Restless legs syndrome-associated intronic common variant in *Meis1* alters enhancer function in the developing telencephalon. *Genome Res.* **24**, 592–603 (2014).
209. Uhl, G. R. & Martinez, M. J. PTPRD: neurobiology, genetics, and initial pharmacology of a pleiotropic contributor to brain phenotypes. *Ann. N. Y. Acad. Sci.* **1451**, 112–129 (2019).
210. Drgonova, J. et al. Mouse model for protein tyrosine phosphatase D (PTPRD) associations with restless leg syndrome or Willis–Ekbom disease and addiction: reduced expression alters locomotion, sleep behaviors and cocaine-conditioned place preference. *Mol. Med. Camb. Mass.* **21**, 717–725 (2015).
211. Lyu, S. et al. The role of BTBD9 in striatum and restless legs syndrome. *eNeuro* https://doi.org/10.1523/ENEURO.0277-19.2019 (2019).
212. DeAndrade, M. P. et al. Motor restlessness, sleep disturbances, thermal sensory alterations and elevated serum iron levels in *Btbd9* mutant mice. *Hum. Mol. Genet.* **21**, 3984–3992 (2012).
213. Freeman, A. et al. Sleep fragmentation and motor restlessness in a *Drosophila* model of restless legs syndrome. *Curr. Biol.* **22**, 1142–1148 (2012).
214. Catoire, H. et al. Restless legs syndrome-associated MEIS1 risk variant influences iron homeostasis. *Ann. Neurol.* **70**, 170–175 (2011).
215. Lyu, S. et al. BTBD9 and dopaminergic dysfunction in the pathogenesis of restless legs syndrome. *Brain Struct. Funct.* **225**, 1743–1760 (2020).
216. Mondello, S. et al. Searching for novel candidate biomarkers of RLS in blood by proteomic analysis. *Nat. Sci. Sleep.* **13**, 873–883 (2021).
217. Garcîa-Borreguero, D. et al. Systematic evaluation of augmentation during treatment with ropinirole in restless legs syndrome (Willis–Ekbom disease): results from a prospective, multicenter study over 66 weeks. *Mov. Disord.* **27**, 277–283 (2012).
218. Oertel, W. H. et al. One year open-label safety and efficacy trial with rotigotine transdermal patch in moderate to severe idiopathic restless legs syndrome. *Sleep. Med.* **9**, 865–873 (2008).

Author contributions

Introduction (M.M. and Y.D.); Epidemiology (K.B.); Mechanisms/pathophysiology (B.S., A.V., Y.D. and M.M.); Diagnosis, screening and prevention (M.M., R.F. and D.G.-B.); Management (D.G.-B., A.V. and Y.D.); Quality of Life (K.B., D.G.B. and Y.D.); Outlook (B.S., M.M. and Y.D.); Overview of Primer (M.M. and Y.D.)

Competing interests

Y.D. participated on the advisory boards for UCB Pharma, Jazz, Theranexus, Avadel, Idorsia, Takeda, and Bioprojet, outside this work. K.B. has received, for a study on the 'Course of Restless Legs Syndrome' (2008–2014), unrestricted grants to the University of Muenster from the German Restless Legs Society and a consortium with equal shares formed by Boehringer Ingelheim Pharma, Mundipharma Research, Neurobiotec, UCB Germany and Switzerland, Vifor Pharma and Roche Pharma. M.M. participated on the advisory boards of Jazz and Avadel, and also received an unrestricted grant from Vifor Pharma and Philips Respironics for the "Life-ON Study" to explore sleep disorders during pregnancy. R.F. participated in educational activities for Jazz. B.S. has received research funding from the German Restless Legs Society and has filed a patent application. D.G.-B. has received research grants from MSDS and Roche, and has consulted for Roche, Idorsia, Luye Pharma, Takeda and American Regent. A.V. declares no competing interests.

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