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REVIEW

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Recent advances in the diagnosis, genetics and treatment of restless legs syndrome

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Abstract Knowledge of restless legs syndrome (RLS) has greatly increased in recent years due to the many advances that have been made in diagnosis, management and genetics. Tools have been developed that facilitate the diagnosis and treatment of RLS, in particular the essential diagnostic criteria for RLS have been refined, severity scales (IRLS, RLS-6, JHSS) have been developed, as have instruments that improve diagnostic accuracy and assess for specific aspects of RLS such as augmentation. These newly developed tools have been used in recent population-based studies, which have provided a greater understanding of the epidemiology of RLS, and also within patient-based trials.

As far as the genetics of RLS is concerned, linkage studies in RLS families have revealed eight loci but no causally related sequence variant has yet been identified using this approach. Recent genome-wide association studies have identified variants within intronic or intergenic regions of MEIS1, BTBD9, and MAP2K5/LBXCOR1, and PTPRD, raising new pathological hypotheses for RLS. An overview on therapeutic options and recent trials is given based on evidence-based management strategies for this common disorder.

Key words restless legs syndrome · RLS · genetics · MEIS1 · BTBD9 · augmentation · diagnosis · treatment · scales

Introduction

Recent years have seen considerable progress in several fields of restless legs syndrome (RLS) research: the essential diagnostic criteria have been refined, new rating scales have been developed, and there have been new discoveries in the field of RLS genetics. Furthermore, an increasing number of well-designed clinical trials on the treatment of RLS has been undertaken and published.

This review examines some of these recent advances, and summarizes evidence-based management strategies for this common disorder.

RLS epidemiology

One area of research that has shed some light on RLS in recent years is the re-examination of the prevalence of RLS in several large epidemiological studies that were able to use the essential diagnostic criteria. There is considerable consistency in the prevalence of RLS in recent European studies (Table 1) with most studies reporting an overall prevalence of RLS up to 10% of RLS symptoms [1–4], and a female preponderance of almost 2:1 [1, 2, 4], which has been shown to be related to parity: whereas nulliparous women had the same risk for RLS as age-matched men, the risk for RLS increased gradually for women with one child (OR, 1.98; 95% CI, 1.25–3.13), two children (OR, 3.04; 95% CI, 2.11–4.40), and

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Table 1 Prevalence of RLS

Study	Country	Number	Population	Prevalence of moderate to severe RLS among sufferers	Methods	Prevalence		
						All	Female	Male
Ulfberg J, et al. (2001) Eur Neurol 46:17–19	Sweden	200	Women, 18–64 yrs	48 % (IRLSSG criteria)	Questionnaires sent to subjects	–	11.4 %	–
Ulfberg J, et al. (2001) Mov Disord 16:1159–1163	Sweden	4000	Men, 19–64 yrs		Questionnaires sent to subjects	–	–	5.8 %
Sevim S, et al. (2003) Neurology 61:1562–1569	Turkey	3234	Adult population		Face-to-face interviews	3.18 %	3.9 %	2.45 %
Hening W, et al. (2004) Sleep Med 5:237–246	USA, Europe (France, Germany, Spain, UK)	23052	Primary care population	35.4 % (twice weekly symptoms with a high negative impact on quality of life)	Survey of matched patients and primary care physicians	11.1 %	–	–
Berger K, et al. (2004) Arch Intern Med 164:196–202	Germany	9310	Adults, 20–79 yrs		Face-to-face interviews & physical examination	10.6 %	13.4 %	7.6 %
Tison F, et al. (2005) Neurology 65:239–246	France	10263	General adult population	56 % (IRLSSG criteria)	Face-to-face interviews	8.5 %	10.8 %	5.8 %
Allen RP, et al. (2005) Arch Intern Med 165:1286–1292	USA, Europe	15391	General population	37 % (twice weekly moderately-severely distressing)	Face-to-face interviews	7.2 %	9.0 %	5.4 %
Hogl B, et al. (2005) Neurology 64:1920–1924	South Tyrol	701	General population, 50–89 yrs	66 % (IRLSSG criteria)	Face-to-face interviews	10.6 %	14.2 %	6.6 %
Bjorvatn B, et al. (2005) Sleep Med 6:307–312	Norway, Denmark	2005	General population, 18–99 yrs	48.4 % (IRLSSG criteria)	Telephone interview	11.5 %	13.4 %	9.4 %
Hadjigeorgiou GM, et al. (2007) Eur J Neurol 14:1275–1280	Central Greece	3033	General adult population ≥ 20 yrs	56.4 % (IRLSSG criteria)	Face-to-face interviews & physical examination	3.9 %	2.8 %	1 %
Ulfberg J, et al. (2007) Sleep Med 8:768–772	Sweden	1000	General adult population, 18–90 yrs	64 % (IRLSSG criteria)	Telephone interview	5 %	5.7 %	3.5 %
Happe S, et al. (2008) J Neurol (in press)	Germany	1312	General adult population, 25–75 yrs	60 % of all RLS cases reported symptoms at least once a week	Face-to-face interviews	8.8 %	10.2 %	7.1 %

three or more children (OR, 3.57; 95 % CI, 2.30–5.55) [4]. The prevalence rates reported from South-eastern Europe are lower: 3.2 % in Turkey [5] and 3.9 % in Central Greece [6].

Some of the more recent studies have incorporated measures of RLS severity or symptom frequency and, therefore, enable the identification of a subgroup of RLS sufferers who are most likely to require treatment [1, 2], as well as providing a specific time frame of prevalence [4]. The severity of RLS according to the IRLSSG in the general population has been shown to be moderate to severe in 35.4 %–66 % of cases [1, 3, 6–8].

Diagnosing RLS

Essential criteria, diagnostic rates and misdiagnosis

In recent years a certain number of tools have been developed to facilitate the diagnosis and treatment of RLS [9]. These include refinement of the essential criteria for RLS, severity scales (IRLS (Table 4), RLS-6, JHSS) [10–12], instruments that improve diagnostic accuracy (RLS-DI) [13], as well as tools for assessing specific aspects of RLS such as augmentation (Augmentation Severity Rating Scale, ASRS) [14]. In 1995 the International RLS Study Group (IRLSSG) established four clinical diagnostic criteria for RLS that were subsequently refined and reviewed during a National Institutes of Health (NIH) workshop in 2002 [15]. The four criteria can be seen in Table 2.

With regard to the rates of diagnosing RLS, a recent population-based survey in Germany, the so-called Dortmund Health Study (n = 1312) with face-to-face interviews in randomly selected participants aged 25–75 years reported the overall prevalence of individuals with a known doctor diagnosis of RLS was 2.3 %; however, an additional 6.5 % fulfilled the four minimal criteria yet were not aware of their RLS. Therefore, the overall prevalence was 8.8 % in this sample and was found to be higher in German descendants than in Turkish migrants (9.2 % vs. 6.7 %) [16]. Whereas in this study the ratio of diagnosed and undiagnosed RLS was 1:3, diagnosis rates were even lower ranging from 3.3 % to 13 % in some of the previous studies [2, 5, 17, 18], and in another study none of the RLS subjects had received a first-line treatment [1]. In light of the proportion of subjects with at least moderate symptoms, as described above, it is remarkable that only 1.6 % of the general population wanted a drug treatment for their RLS [16].

In the European context, the lowest diagnosis rate for RLS was reported from the UK: in a general practice research database involving 1,561,692 patients, the prevalence of RLS with a registered diagnosis of RLS was only 0.25 %. This was not based on either a specific RLS questionnaire or specific interviews. Only 0.6 % of these had received a prescription for levodopa or a dopamine agonist, while many were prescribed medications not effective in RLS (principally oxerutins and quinine in that study) [19]. The prescription of phlebotonics and crampolytics in RLS points to a high rate of misdiagnosis. This is further supported by the French epidemiological survey, where 60 % of the RLS affected individuals had received a previous vascular diagnosis [2], an Irish study where only 16.7 % of RLS sufferers were diagnosed with RLS [20], and the REST studies, where patients with RLS had been given a diagnosis of lower back pain, depression, peripheral neuropathy, spinal problems and transferred to orthopedics, vascular surgeons, psychiatrists and other specialists [18].

Whereas the four diagnostic criteria can be easily confirmed by history, and even a single screening question based on these essential criteria has been reported to have a good sensitivity and specificity [21], the diagnostic certainty can be improved if supportive clinical criteria for RLS are present or if additional tests can be obtained [22]. Supportive clinical features include a positive levodopa response, which has been translated into a diagnostic levodopa test for RLS [23]. Periodic limb movements have been reported to be present during sleep in 80 % to 85 % of RLS patients, and PLM during wakefulness are considered even more sensitive and specific for RLS [24]. The presence of a positive family history is also useful to support the diagnosis of RLS (Table 3) [15]. The exclusion of mimics requires that a physician who is well trained in RLS sees the patient in person or interviews them on the phone [25].

In light of the still frequent under- and misdiagnosis of RLS, it should be mentioned as well that some of the prevalence rates reported in older studies may have been too high due to the use of inappropriate single questions not reflecting the consensus clinical criteria and also by

Table 2 Essential diagnostic criteria [15]

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs).
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or 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 or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been present previously).

Table 3 Supportive criteria and associated features of RLS [15]

- Family history
- Response to dopaminergic therapy
- Periodic limb movements (during wakefulness or sleep)
- Natural clinical course
- Sleep disturbance
- Medical evaluation/physical examination (It is important to look at conditions that may exacerbate RLS, and the presence of peripheral neuropathy and radiculopathy should also be determined)

Table 4 Severity Scale of the International RLS study group (IRLSSG) [10]

1. Overall, how would you rate the RLS discomfort in your legs or arms?
2. Overall, how would you rate the need to move around because of your RLS symptoms?
3. Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?
4. Overall, how severe is your sleep disturbance from your RLS symptoms?
5. How severe is your tiredness or sleepiness from your RLS symptoms?
6. Overall, how severe is your RLS as a whole?
7. How often do you get RLS symptoms?
8. When you have RLS symptoms how severe are they on an average day?
9. Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work life?
10. How severe is your mood disturbance from your RLS symptoms – for example, angry, depressed, sad, anxious or irritable?

"RLS mimics". An interview with a trained physician is necessary for the correct diagnosis of RLS: if only questionnaires with the RLS criteria are given to patients this results in approximately 10–25 % false positives due to "RLS mimics" [26, 27]. Patients with RLS mimics meet all the essential diagnostic criteria but do not actually have RLS. Important mimics include akathisia, positional discomfort, cramps, peripheral neuropathy and anxiety disorders [26]. RLS also needs to be differentiated from other conditions that can also coexist with it such as peripheral neuropathy, lower limb pain conditions of different origin, parkinsonism with sensory symptoms or motor fluctuations with dyskinesias, etc. It is assumed that the high prevalence of RLS in the Parkinson's disease population is, at least in part, due to mimics or overlap with RLS – with symptoms easily confounded for a patient with RLS, such as peak-dose or biphasic dyskinesia, akathisia, and early morning dystonia [28, 29]. One group has coined the term RLS – like syndrome for depression mimicking RLS [30]. In some cases, however, RLS and depression coincide [31].

Diagnosing RLS in children and the elderly

In children, diagnosis of RLS can be a challenge, when a clear verbal description cannot be given. Growing pains and attention deficit hyperactivity disorder (ADHD) are important differential diagnosis [32]. If a clear verbal description cannot be given, the diagnosis in children can be supported by a positive family history or a PLM index > 5 per hour in overnight polysomnography [15, 33]. In contrast, in elderly patients with cognitive impairment, diagnosis may be difficult when memory or language problems hinder a proper history taking. In this patient group, the consensus paper recommends referral for observation, e.g., leg kicking and pacing in the evening, holding the legs and rubbing them, etc. [15].

Diagnostic tests

Whereas the performance of a routine laboratory examination including tests for renal function and thyroid parameters are considered standard in RLS, the importance of performing a complete evaluation of the iron status (in contrast to only performing a red blood cell count) cannot be overemphasized. A complete iron status involves measures of iron, serum ferritin and transferrin saturation, if possible also total iron binding capacity. Because of the comparatively low value of serum ferritin determinations to indicate the state of body iron stores [34], and the influence of inflammatory states on serum ferritin, alternative methods for determining body iron states have been searched. The soluble transferrin receptor has been considered a more sensitive measure of low body iron stores and proved useful in RLS [1]; however, its use is limited by the high cost. If a full iron status cannot be obtained, the minimal requirement is to perform a serum ferritin analysis.

Polysomnography is not required in all RLS patients, but useful in patients with other sleep-related comorbidities. PLM indices have been frequently used to indicate treatment response of RLS. In light of the increasing understanding of the relationship between PLM and high blood pressure [35] and sleep [36, 37], and the close relationship between RLS genes and PLM [27], it is likely that actigraphy will be used more frequently in the future. However a manual set of threshold and visual inspection of data are prerequisite for obtaining valid and reliable PLM indices from actigraphy [38].

Other objective tests include midbrain sonography [39, 40], neuroimaging [41, 42], and cerebral spinal fluid (CSF) tests [43–45], but these remain tests to be carried out for research purposes and are not currently useful for the diagnosis of RLS in the clinical setting.

Genetics of RLS

RLS is a highly familial phenotype with heredity estimates of about 50 % [46–48]. In comparison to non-familial cases, familial RLS usually has a younger age at onset [46–49] and has a more slowly progressive course [50]. The symptoms within a single RLS family can be variable with some individuals only displaying symptoms a few times throughout their lives, while severely affected family members suffer from restlessness and sleep disturbances.

Linkage studies in RLS families have revealed eight loci but no causally related sequence variant has yet been identified using this approach. Based on the assumption that the disease follows a recessive mode of inheritance, linkage to chromosome 12q (RLS1) was identified in a French-Canadian family [51]. Further studies in Italian, US, Canadian and German families showed linkage to chromosome 14q (RLS2), 9p (RLS3), 20p (RLS4), and 2q (RLS5) using a dominant model of inheritance [52–55]. Two loci were identified in a single RLS family on chromosome 4q and 17p under the assumption of an autosomal-dominant model [55] and suggestive evidence for linkage was found on chromosome 19p [56]. The existence of RLS1–3 is further supported by independent families [57–61], and there is evidence for further genetic heterogeneity.

A candidate gene approach was performed in a French-Canadian population of 92 cases and 182 controls, genotyping functional polymorphisms in MAOA and MAOB [62]. These enzymes are involved in the dopamine catabolism through oxidative deamination and certain polymorphisms are correlated with different enzyme activities [62]. A “high activity allele” of MAOA was only associated to RLS in females but not in males. So far this observation has not been replicated in independent samples.

Association studies compare the frequencies of alleles in case and control populations. A higher frequency of the allele tested in cases is taken as evidence that the allele or genotype is associated with an increased risk for the disease [63].

A systematic hypothesis-free approach was performed in an association study of two Caucasian RLS samples of altogether 918 cases and controls. A total of 1536 single nucleotide polymorphisms (SNPs) in 366 genes encompassing a 21 Mb region of the RLS1 locus were analyzed. Significant association to the neuronal nitric oxide synthase (NOS1) was identified. Analyzing single associated SNPs within NOS1 showed different allele frequencies with in part opposite directions [64]. This implies that the same allele is a risk allele in one sample but a protective allele in the other, which is difficult to interpret. Therefore, further studies in independent populations are needed to replicate this finding. The association of variants in the NOS1 gene and RLS, however, suggests an involvement of the NO/arginine pathway in the pathogenesis of RLS.

Two recent studies used a large-scale high-density genome-wide approach. In a study conducted in the German and Canadian population in a total of 1600 RLS cases and 2600 controls, three genomic regions were identified encoding the genes MEIS1, BTBD9 and a third region containing MAP2K5 and LBXCOR1 [65]. Association was identified to intronic variants, which suggests a role in the expression or alternative splicing of the gene. Carriers of one risk allele had a 50 % risk increase of developing RLS. In a similar study conducted in the Icelandic and US population an association was found to the identical variant in BTBD9 [27]. Both studies used different assessments of the phenotype. In the German/Canadian study all individuals underwent a personal interview conducted by an RLS expert. To minimize phenotypic heterogeneity only cases with a positive family history were included. The Icelandic study used a standardized diagnostic interview. In a preceding validation study of the interview a false positive rate of about 20 % was elucidated. Therefore, a combination of parameters was used to define the phenotype more accurately. The presence of PLM was used to additionally support the diagnosis of RLS and the association to BTBD9 was based on PLM-positive individuals. However, this still does not answer the question whether PLM should be included as a diagnostic criterion for RLS in genetic studies. PLM can also occur in other disorders, such as in isolated PLMD, narcolepsy or Parkinson’s disease. It remains to be investigated whether this variant is also associated to individuals with these disorders and reporting PLM. Furthermore, an analysis of parameters involved in iron metabolism revealed that the risk allele showed a 13 % decrease of the serum ferritin level and one interesting question is whether the variant identified in the German Canadian study was also associated to serum ferritin. Only recently, a further

association study including about 2500 cases with RLS and 5000 controls focused on the RLS3 linkage regions. Two independent signals within splice variants expressed in the central nervous system of PTPRD showed genome-wide significant association to RLS [66].

A closer inspection of the known function of the genes identified is surprising as some of them are developmental factors. MEIS1 is a member of a family of highly conserved TALE homeobox transcription factors. MEIS1 is part of a transcriptional regulatory network that specifies spinal motorneuron pool identity and connectivity and therefore may have a function in the motor part of RLS or PLM [67]. A study in xenopus showed that MEIS1 is also involved in neural crest development [68]. The third region encoded the MAP2K5 gene, a member of the mitogen-activated protein kinase family, and the adjacent LBXCOR1 gene. LBXCOR1 is annotated downstream of MAP2K5 acting as a transcriptional corepressor of LBX1. This homeobox gene plays a critical role in the development of sensory pathways in the dorsal horn of the spinal cord that relay pain and touch [69]. Both genome-wide association studies showed association to BTBD9. Little is known about BTBD9 other than that it belongs to the BTB(POZ) domain-containing proteins. Functions of BTB(POZ) proteins include transcription repression, cytoskeleton regulation, tetramerization and gating of ion channels as well as protein ubiquitination/degradation [70]. The modular nature of this protein and the universal occurrence of the particular domains of BTBD9 make an assignment of a specific function difficult at present [65]. PTPRD encodes a Protein Tyrosine Phophatase receptor Type Delta. The involvement of PTPRD in RLS is unknown. Studies in PTPRD and PTPRS knockout mice have shown that these proteins function in axon guidance and termination of mammalian motorneurons during embryonic development [71].

Subanalysis of endophenotypes can give a better understanding about the genes associated with a specific symptom of RLS. It is likely that investigations in larger sample sizes are going to identify further variants associated with RLS. This will enable the identification of even smaller effects. The European RLS Study Group has initiated a project named EU-RLS-GENE that seeks to identify RLS susceptibility genes by investigating RLS families, sibling pairs and trios. A question that needs to be solved is whether RLS has components of a developmental disorder and whether the genes identified play a role in early embryonic days or have a completely different function in the elderly and in association to RLS. The variants identified are common and confer small to moderate relative risk. The identification of a rare and strong "monogenic" variant responsible for RLS in families is another challenge in the research of RLS.

Management of RLS

General aspects of treating RLS patients

The high prevalence of RLS does not necessarily mean that all patients with RLS should be treated with pharmacological therapy, since patients with sporadic or only mild symptoms who do not experience significant impairment are likely not to require pharmacological treatment. The proportion of those patients within the whole RLS population is currently the subject of ongoing studies. Based on previous results it is estimated that approximately 2–3 % of the population have RLS that is severe enough to merit treatment [17, 18]. A recent epidemiological study in Germany reported that among 1312 participants the prevalence of RLS was 8.8 %; and 1.6 % of the whole study population had a wish for treatment [16]. There are no data available about mild or intermittent RLS and its response to common treatment concepts. Before starting pharmacological treatment, however, sleep hygiene measures should be recommended and all causes of secondary RLS, such as iron deficiency, should be excluded. Data from a central laboratory within treatment trials are not available, therefore, a proper limit of serum ferritin values that require iron supplementation cannot be given. Patients with serum ferritin values even in the low normal range may benefit from iron supplementation (normal serum ferritin [SF]): $100 \pm 60\,\mu g/L$; iron depletion, $< 20\,\mu g/L$; in RLS patients SF $< 50\,\mu g/L$ should be corrected) [72]. A recent study has shown that such patients exhibit increased rates of augmentation on dopaminergic therapy [73].

Based on clinical trials and expert experience, long-term therapy with only one substance at a stable dosage may cause increasing problems over time. Therefore, the best strategy is to start pharmacological therapy cautiously and at the lowest recommended dosage. On the other hand, RLS and the related chronic sleep disturbance it causes may significantly impact sleep, social and working life [74–76], and adequate treatment should therefore not be withheld from those patients in need.

Pharmacological intervention in RLS is symptomatic and can relieve subjective symptoms or improve the sleep disorder or both.

Non-pharmacological treatments such as exercise [77] have rarely been investigated and their efficacy has not been demonstrated according to evidence-based medicine (EBM) criteria. Evaluation of those treatments will be given in a review on treatments according to EBM in RLS [78]. Recently, approaches for additional psychotherapeutic interventions have been described and are currently under investigation in clinical trials [79].

According to EBM criteria, dopaminergic therapy should be the first-line therapy in RLS [78], as recommended in guidelines issued by several societies [80–82], although the precise mode of action is unknown.

Levodopa/decarboxylase inhibitor (DDCI)

Eight randomized controlled trials [83–90] are available to prove the efficacy of levodopa/DDCI in RLS therapy. Four of these trials are placebo-controlled mostly giving levodopa/DDCI as a single bedtime dose for nocturnal RLS symptoms [83–85, 88]. Two trials, including an open study, have investigated the sustained release formulation of levodopa [87, 89], while four trials have investigated levodopa compared to other agents such as pergolide [86], valproic acid [89], gabapentin [91], and cabergoline [90]. The dosages range between 100–300 mg per night as a single dose, with a second dose three hours after bedtime or in combination with a sustained-release formulation. Levodopa controls the motor and sensory disturbances of RLS as measured by subjective RLS rating scales and reported better quality of life with improved severity of RLS [84]. Polysomnographic parameters also improved [83, 84, 92]. A comparative trial with cabergoline (1–3 mg, compared with up to 300 mg levodopa) showed the superiority of cabergoline in relation to measured efficacy and with less augmentation. However, fewer side effects such as nausea and dizziness were reported with levodopa.

Levodopa is a short-acting medication and it therefore seems to be an appropriate substance for treating mild and intermittent RLS, although all treatment trials with levodopa to date have been performed including all forms of RLS severity. Levodopa/benserazide is licensed for RLS therapy in Germany, Switzerland, Austria, Croatia, Poland, and Brazil. The limitation of levodopa consists mainly of its long-term side effect with augmentation (see below).

Dopamine agonists

Ergot-dopamine agonists

The ergot-dopamine agonists, bromocriptine, pergolide and cabergoline, have been investigated in RLS therapy and have all proven effective according to EBM level-1 studies [78].

Bromocriptine was the first DA used in RLS therapy. A double-blind controlled study with a long-term observation of 1 year showed that pergolide was efficacious at dosage of 0.05–0.65 mg/day. The IRLS score improved in a large multicenter (PEARLS) study with 100 patients, (IRLS score 12.2 pergolide *vs.* 1.8 placebo) [93]. After 12 months of double-blind therapy with pergolide, improvements in the PLMS arousal index and the PLMS index were maintained, but no significant improvements were seen in sleep efficiency (11.3 % vs. 6.1 %; P = 0.196) or total sleep time (TST; P = 0.145). For cabergoline, the largest trial was a trial with levodopa in 361 patients with severe RLS, comparing 2–3 mg cabergoline (n = 178) and 200/50–300/75 mg levodopa/benserazide (n = 183) (CALDIR study) [90]. Both treatments were efficient according to subjective rating of the IRLS. Augmentation has been reliably assessed by clinical interviews in several trials revealing a lower incidence compared to levodopa. No special concerns about "sleep attacks" have been raised in trials with dopamine agonists in RLS compared to those in Parkinson disease.

In the past years, increasing knowledge about valvular fibrosis as a side effect of the ergot-DA has been gathered [94]. This side effect has been associated with 5-HT2B agonist/stimulant effects of most ergot DAs [95]. Therefore, it is important to mention the currently used ergot DA lisuride. Lisuride behaves as a 5-HT2B receptor antagonist and is also a strong 5-HT1A agonist. It has been investigated as a transdermal patch (fixed dose 3 mg or 6 mg) in a small 1-week randomized, double-blind, parallel treatment with nine patients and was found effective (1 patch, 3 mg: IRLS – 23.3 ± 11.6; 2 patches, 6 mg: IRLS – 22.0 ± 12.5) [96].

Non-ergot dopamine agonists: ropinirole, pramipexole, rotigotine

Seven randomized, placebo-controlled trials [97–103] (Level-I [78]) have been reported with ropinirole in the treatment of RLS, four of them large-scale clinical trials. In a sleep lab trial there was a significant decrease in sleep laboratory parameters including PLMS/h and PLM arousals/h; sleep efficiency was not different from placebo-treated patients [104].

In two 12-week prospective, double-blind, placebo-controlled trials, over 550 patients (age 18–79 yrs) with RLS having an IRLS score of ≥ 15 were treated with 0.25–4.0 mg/day ropinirole administered 1–3 hours before bedtime or placebo, confirmed by a third study using a similar design [97–103]. Improvement in IRLS scores at week 12 was greater in the ropinirole group (mean [SD] dose, 1.90 (1.13) mg/day) compared with placebo. Secondary end points, i.e., subjective sleep scales, also improved. In a withdrawal design Montplaisir et al. [105] investigated the long-term efficacy of ropinirole in patients who received the drug for 24 weeks in an open study before being randomized to double-blind treatment with either ropinirole or placebo for a further 12 weeks. Significantly fewer patients relapsed on ropinirole than on placebo.

Currently, over 1000 patients with idiopathic RLS have been included in controlled trials with ropinirole. Adverse reactions were similar to those reported for ropinirole in Parkinson's disease studies and included nausea, somnolence and dizziness. No cases of dyskinesia or sleep attacks were observed. Patients were usually followed for 12 weeks, in sleep laboratory studies some for only 4 weeks. The mean effective daily dose of ropinirole reported in clinical trials was about 2 mg, which

is currently used in clinical practice as a single dose at night, but often also used in divided low dosages when patients complain about evening symptoms.

For pramipexole treatment in RLS, five randomized, placebo-controlled trials [106–110] (Level-I [78]) have been published, the first small study using sleep lab outcome measures by Montplaisir et al. [106]. In a further polysomnographic study, Partinen et al. [107] investigated 109 patients for 3 weeks in a double-blind, placebo-controlled dose-finding study. Pramipexole improved PLM index and IRLS scores significantly. Winkelman et al. [108] and Oertel et al. [110] confirmed in their 6-week randomized, placebo-controlled trials with over 300 patients, respectively, with fixed doses (0.25, 0.50 or 0.75 mg) or flexible doses (0.125–0.75 mg pramipexole per day) the results from previous trials.

In a controlled withdrawal study (n = 150 RLS patients who had responded to pramipexole, mean dose, 0.50 mg) [109], significantly more patients on placebo experienced a worsening in their symptoms compared to patients receiving pramipexole and withdrew from the study because of loss of efficacy with placebo.

Over 1000 patients with idiopathic RLS have been included in controlled trials that were all in favor of pramipexole; adverse reactions were similar to those reported for pramipexole in Parkinson's disease studies and included nausea, somnolence and dizziness. So-called sleep attacks and increased sleepiness were not observed within the clinical trials and especially in one retrospective study, which is different from trials in Parkinson's disease patients [111]. The mean dosage in pramipexole trials was between 0.25 and 1 mg (= 0.18 and 0.70 mg pramipexole base) and this reflects the current clinical use of the drug in RLS.

Rotigotine, a D3/D2/D1 dopamine agonist developed as a matrix-type transdermal patch for once-daily dosing has been studied for treating RLS. In addition to a dose finding trial [112], two double-blind, multi-center controlled trials with rotigotine including more than 300 patients treated with a dose of 1.125 mg/day, 2.25 mg/day and 4.5 mg/day showed a significant improvement on the IRLS compared to placebo for all dosages [112, 113]. In the recent multi-center trial the lowest efficient dosage was 1.0 mg rotigotine efficacious per day [114]. In addition to well-known side effects of dopaminergic substances, local site reactions occurred in up to 42 % of patients, most of them were mild and did not lead to drop-out from the trial.

General considerations for dopamine agonists: A more detailed prospective analysis of augmentation and side effects such as dopamine dysregulation syndrome (DDS), sleepiness or sudden sleep onset would be required in long-term studies.

Ropinirole is licensed for RLS therapy in the countries of the European Union as is pramipexole, but availability has not been implemented in all countries. Rotigotine patch has filed for an indication in RLS therapy in Europe.

Opiates

Opiates have been used for treating RLS as early as Thomas Willis described the first case of RLS treatment in 1684 [115]. Despite the ancient knowledge, data on opioidergic therapy in RLS are rare and not one large-scale trial has been conducted to date. Opioids are regarded as the medication of second choice. In patients who cannot tolerate dopaminergic agents, they are considered the first-choice medication. Although only case reports are available, many patients with more severe forms of RLS have been efficiently treated with a combination of dopaminergic agents and an opioid.

Only one double-blind randomized crossover trial with oxycodone (mean dosage 15.9 mg) reduced sensory symptoms and motor restlessness at night and during daytime [116]. A significant reduction in the PLMS and PLMS arousal index was found polysomnographically. A second double-blind study of opiates in PLMS found a low dose of propoxyphene, which is a less potent opioid than oxycodone, to be effective – though less effective than levodopa – in the treatment of PLMS [117]. Long-term observations are only available as case series [118] and show a minimal risk of dependency, but some worsening of sleep apnea on chronic opioids may occur [118]. Due to the multiple effects of opioids on respiration in sleep, cardiorespiratory monitoring or polysomnography should be performed in at-risk patients such as the elderly or those who are overweight when on long-term treatment with these substances [119, 120]. Long-term trials are needed, but also short-term trials should elucidate which patients may benefit from a continuous opioid treatment and if a respiratory screening evaluation is necessary before opioid treatment is started.

Gabapentin and other anticonvulsants

Gabapentin has been shown to be an effective treatment for RLS [103, 121, 122], although as is the case with opioids, large-scale trials and long-term observations are lacking. To recommend anticonvulsants as first-line treatments for RLS therapy, head-to-head trials with dopaminergics and a better exploration of long-term side effects in RLS patients are necessary.

In a controlled study with a mean dosage of 1855 mg/day [121] the IRLS was significantly improved compared to placebo. In hemodialysis patients, a reduced dosage of 200–300 mg is recommended [122].

Anticonvulsants such as carbamazepine and valproic acid, which have been previously investigated for the treatment of RLS, are no longer regarded as first-line

treatments due to their side effect profile. Early controlled studies with small numbers of patients showed significant effects on treating RLS; the outcome measures, however, are not comparable to recent trials with dopaminergic agents [123, 124].

Benzodiazepines and other hypnosedatives

For clonazepam (dosage 0.5 mg), only small trials are available, mostly with a population of RLS and PLMS patients [125–128]. No recent trials using the current definition criteria and scales have been performed. In those trials a dosage of 0.5 mg clonazepam was not effective for improving either polysomnographic or subjective RLS parameters. Zolpidem and triazolam investigated in a trial with RLS/PLMS patients were not effective either [129, 130].

Iron: oral iron and intravenous administration

To treat RLS patients with iron it is necessary to differentiate between subjects with normal or low iron storage. Unfortunately, only small studies with different compounds are available and data cannot therefore be compared. In a randomized, double-blind, placebo-controlled trial that did not select patients according to their iron status measured by serum ferritin levels, iron sulfate did not improve RLS symptoms [131].

In another study, high-dose iron dextran infusion was associated with a significant, but transient, reduction in symptoms of RLS in patients with end-stage renal disease [132]. In a single open study, in which 10 RLS patients received a single 1000 mg intravenous iron infusion, 7 of them showed a substantial improvement in RLS symptoms 2 weeks later [133]. In 18 RLS patients, 200 mg t.i.d. of oral ferrous sulphate for 8–20 weeks therapy was efficient in those RLS patients who had a serum ferritin $< 45\,\mu g/L$ at baseline.

Two further studies investigated the effect of intravenous iron and found that 1000 mg iron dextran was superior to placebo up to 4 weeks in 25 RLS patients with chronic renal failure. One patient in a short-term study with intravenous iron dextran had a possible allergic reaction (shortness of breath) [133]. A recent trial with intravenous iron sucrose (1000 mg) failed to show any efficacy on clinical symptoms and MRI measured brain iron content in a short-term trial [134].

Intravenous iron studies have to be carefully monitored and further research for patient selection is needed. Although most RLS patients with low serum ferritin values are treated orally with iron, no major trials on oral iron substitution are available in RLS.

Further therapies

Several agents have been tested in open trials or case series, but have not been studied in any controlled or large scale trial or have not been proven sufficiently efficacious in appropriate trials or have shown unfavorable side effect profiles at higher dosages according to EBM [78]: these substances are clonidine [135], amantadine [136], and magnesium [137].

Insufficient response or dopaminergic treatment complications

While the usually excellent treatment response to dopaminergic agents has contributed to dopaminergic systems being long thought of as the main pathogenetic mechanisms in RLS, and a positive response to levodopa can strengthen the diagnosis of RLS [23, 138], in some cases the response can decline over time or symptoms even worsen dramatically.

Tolerance

Tolerance to treatment has been described in some cases of dopaminergic therapy [27] as the loss of therapeutic efficacy of an RLS treatment that had previously been efficacious. It may occur in other RLS therapies as well, but has not been described as such in the current literature.

Rebound

Rebound should be distinguished from augmentation. Rebound is first noticed in the morning with increases of both sensory symptoms and was first described with levodopa [139]. In clinical practice, the relevance of rebound phenomenon is questionable and mostly covered by the occurrence of augmentation.

Augmentation

The most important complication of dopaminergic therapy is augmentation (see definition and measurements above). Augmentation is assumed to be a specific problem associated with dopaminergic medications, although two case reports are documented with possible augmentation under tramadol [140, 141]; the mechanisms underlying the development of augmentation are still under debate [142]. A dopaminergic overstimulation of the striatal dopamine D1-receptors, as happens with levodopa, may play a key role in the development of augmentation [143]. Low serum ferritin levels may enhance the symptoms of augmentation [73].

The clinical features of augmentation were first described by Allen and Earley, who defined augmentation as an earlier onset of symptoms in the afternoon or evening, a quicker onset of symptoms at rest, and an increased intensity and a spread of symptoms to different body parts – usually the arms, but also the trunk and even the face [144]. Due to behavioral coping, augmentation can occur without the patients indicating a clear earlier occurrence. Treatment with long-acting substances or those with continuous delivery giving stable plasma levels could cause augmentation to manifest in a different form that is, without a clear earlier occurrence of RLS symptoms. A recent consensus conference identified five major diagnostic features of augmentation and placed an important focus on paradoxical response to treatment (Table 5) [145].

Predisposing factors for augmentation

Augmentation has been reported more frequently in patients on levodopa therapy than in those on dopamine agonists. However, it is impossible to compare the augmentation rates reported from most previous studies because very different modes of assessment and definitions have been used. The first consensus criteria for augmentation were only agreed upon in 2002 [15] and many of the previous reports on augmentation are based on retrospective chart study. Many of the previous clinical trials have failed to account for augmentation at all or report it as investigator-based adverse event reporting. Only the most recent clinical trials on the treatment of RLS use an adequate methodology for assessing augmentation have been included (see treatment section). In spite of the difficulty of comparing augmentation rates from different studies it has become evident that higher dopaminergic doses must be considered a risk factor for augmentation [144, 146]. Furthermore, a large variation of augmentation rates has been reported with a single substance (e.g., levodopa 9.8 %–72 %) [90].

There is controversy whether a positive family history or an absent family history of RLS is predictive of predisposing for augmentation, as is the question of whether secondary RLS or on the contrary the lack of neuropathy are predictive [146, 147]. Whereas previous augmentation was first reported as a risk factor for the reoccurrence of augmentation in a retrospective study [148] this has not been confirmed in the pooled data from a double-blind, placebo-controlled study [149].

Apart from dose, the only identified risk factor for the occurrence of augmentation (and, for study drop-out due to augmentation) is low serum ferritin at the beginning of dopaminergic treatment [73]. This was con-

Table 5 Max Planck (MPI) diagnostic criteria for augmentation [145] (Reprinted with the kind permission of Elsevier and *Sleep Medicine*)

Augmentation is a worsening of RLS symptom severity experienced by patients undergoing treatment for RLS. The RLS symptoms in general are more severe than those experienced at baseline.
A Basic features (all of which need to be met)
1. The increase in symptom severity was experienced on five out of seven days during the previous week.
2. The increase in symptom severity is not accounted for by other factors such as a change in medical status, lifestyle or the natural progression of the disorder,
3. It is assumed that there has been a prior positive response to treatment.
B Persisting (although not immediate) paradoxical response to treatment: RLS symptom severity increases some time after a dose increase, and improves some time after a dose decrease
OR
C. An earlier onset of symptoms
1. An earlier onset by at least 4 h.
OR
2. An earlier onset (between 2 and 4 h) occurs with one of the following compared to symptom status before treatment:
a. Shorter latency to symptoms when at rest;
b. Spread of symptoms to other body parts;
c. Greater intensity of symptoms (or increase in periodic limb movements, PLM, if measured by polysomnography, PSG, or the suggested immobilization test, SIT);
d. Shorter duration of relief from treatment.
Augmentation requires criteria A+B, A+C or A+B+C to be met.
Augmentation is clinically significant when at least one of the following occurs:
a Change in daily activities and/or behavior (e.g. the patient stops riding in cars in the afternoon) due to augmentation;
b Negative impact on the patient´s quality of life (sleep, mood, etc.) due to augmentation;
c Need to change the treatment dose or the patient needs to take the dose earlier in the day (e.g. dividing the dose);
d Adjustments in concomitant medication are made to compensate for augmented RLS symptoms (e.g. an increased intake of analgesics or hypnotics to cover an increase in symptom intensity);
e Any other aspect as judged by the evaluator (should be specified).

firmed in another recent study [150]. In line with a higher dose as a predisposing factor for augmentation is the concept of a severely increased dopamine concentration in the CNS, which leads to an overstimulation of the pronociceptive spinal dopamine D1 receptor compared to the antinociceptive D2 receptors in the spinal cord.

Conflicts of interest Birgit Högl, MD, has been an advisor and/ or speaker for Boehringer Ingelheim GmbH, GlaxoSmithKline, UCB, Pfizer, Jazz, Merck and Cephalon. Juliane Winkelmann, MD, has been a speaker for Boehringer Ingelheim GmbH, GlaxoSmithKline, and Hoffmann La Roche. Claudia Trenkwalder, MD, has been a speaker for Boehringer Ingelheim GmbH, GlaxoSmithKline, UCB, Pfizer and Hoffmann La Roche. She has received consultant honoraria from Boehringer Ingelheim GmbH, UCB, Novartis, Orion Pharma and Solvay.

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