Restless legs syndrome: differential diagnosis and management with rotigotine

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Abstract: RLS is a common sleep disorder with distinctive clinical features. The prevalence of RLS in Caucasians and North Americans ranges from 5% to 10%. However, only some of these subjects (almost the 3% of the general population) report being affected by a frequent and severe form of the sleep disorder. RLS is diagnosed clinically by means of four internationally recognized criteria that summarize the main characteristics of the sleep disorder. Besides the essential criteria, supportive and associated features of RLS have been established by experts in order to help physicians treat patients with doubtful symptoms. Several clinical conditions may mimic this sleep disorder. In order to increase the sensibility and specificity of RLS diagnosis, doctors should perform a meticulous patient history and then an accurate physical and neurological examination. Dopamine agonists are recognized as the preferred first-line treatment for RLS. Rotigotine is a non-ergoline dopamine agonist with selectivity for D1, D2 and D3 receptors. The drug is administered via transdermal patches which release rotigotine for 24 hours. Four clinical trials demonstrated that this compound is able to improve RLS symptomatology with few and moderate adverse events. Head to head trials are required to compare the efficacy and tolerability of rotigotine with other dopamine agonists administered via oral intake. Rotigotine has been approved by the FDA and EMEA for Parkinson's disease. For the treatment of moderate to severe idiopathic RLS, rotigotine has been recommended for approval by the EMEA and is under review by the FDA.

Keywords: restless legs syndrome, diagnosis, differential diagnosis, dopamine agonists, rotigotine

Introduction

Restless legs syndrome (RLS) is included in the most recent version of the International Classification of Sleep Disorders (ICSD-2) among the sleep-related movement disorders.[1] Patients with RLS report an urge to move their legs caused or accompanied by unpleasant sensations in the affected limbs. The urge to move appears at rest and is improved by leg movements. RLS symptoms show a classic circadian pattern appearing or worsening in the evening or during the night.[2]

To date, the underlying pathophysiology of RLS is still not fully understood. The most accredited hypothesis recognizes an involvement of the diencephalic A11 dopaminergic neurons. It seems that these dopaminergic cells are able to modulate the nociceptive afferents by means of their projections into the dorsal horns of the spinal cord.[3,4] Specific lesions in A11 nuclei of rats induced some features similar to those of human RLS with a long latency of sleep, a reduced sleep time, and several episodes of standing upright. As for RLS symptomatology, these abnormal behaviors decreased after pramipexole treatment.[5] In a subsequent study, locomotor activity was evaluated in four groups, consisting of: normal mice, mice with A11 lesions, mice fed with a low-iron diet, and mice with A11 lesions combined with iron deprivation. Locomotor activity was increased in both the A11-lesioned and iron-deprived mice compared with normal mice. In the group

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combining A11 lesions with iron deprivation, the mice showed further augmented motor activity.[6] An increased locomotor activity during either the end of the active or during the inactive period, similar to human RLS, has been recently observed in other animal studies characterized by dietary iron deprivation.[7,8] The role of iron status on RLS pathophysiology has been largely evaluated also in humans. A reduced brain iron content was noticed in RLS patients during autopsies, magnetic resonance and transcranical ultrasound imaging studies, and cerebrospinal fluid analyses.[9–13] Clinical conditions, such as pregnancy, end-stage renal disease and gastrectomy, that are able to compromise iron availability, favor the occurrence of RLS. In fact, patients with decreased peripheral iron stores have a higher risk of reduced iron status in the central nervous system than the general population. Brain iron deficiency might cause abnormalities in dopaminergic systems and, consequently, induce RLS symptoms.[14]

RLS can be distinguished in primary and secondary forms. To diagnose a primary form of RLS, all the clinical conditions known to favor the sleep disorder have to be ruled out by laboratory, physical, neurological and neurophysiological examinations. The main characteristic of primary RLS is a positive family history;[15] thus a genetic basis for this form has been hypothesized.[16] Linkage studies demonstrated the presence of 5 different loci associated with RLS (RLS1 on chromosome 12q, RLS2 on chromosome 14q, RLS3 on chromosome 9p, RLS4 on chromosome 2q, RLS5 on chromosome 20p).[17–26] A part from RLS1 that showed a pseudodominant pattern of inheritance, the remaining loci were identified under the assumption of an autosomal dominant model. In addition, other 3 loci on chromosome 19q, 4q and 17p were recently identified.[27,28] The large number of loci associated with RLS point to genetic heterogeneity of the sleep disorder. The role of these genome-wide linkage studies in improving our knowledge of RLS has been very limited. More interesting information came from genome-wide association studies. These analyses identified variants within intronic and intergenic regions of *MEIS1*, *BTBD9*, *MAP2K5/LBOXCOR1* and *PTPRD*.[29–31] Subjects carrying one allele-risk have a 50% increased risk of developing RLS.

Iron deficiency, end-stage renal disease, peripheral neuropathy, use of neuroleptics and pregnancy represent the clinical conditions identified as risk factors for RLS.[32] Recently, type 2 diabetes mellitus and multiple sclerosis have been recognized as being able to favor RLS.[33,34] Patients affected by secondary forms of the sleep disorder report a low frequency of positive family history of RLS, a late age of onset of RLS, and the antecedence of onset of the main clinical condition to RLS onset. In addition, a treatment able to remove the main clinical condition (such as iron supplements and kidney transplantation) may produce a complete remission of RLS symptomatology.

In patients affected by RLS with a serum ferritin concentration lower than 50 μg/L, iron therapy should be started. Since oral iron is not well absorbed by the gastrointestinal tract, intravenous iron infusions are considered more effective in treating this secondary form of RLS.[35–37] However, a recent randomized, double-blind, placebo-controlled study of 1000 mg intravenous iron sucrose failed to demonstrate significant improvements in RLS symptoms.[38] Moreover, in almost 3% of subjects treated with intravenous iron dextran an anaphylactoid reaction may occur. This risk is increased in patients affected by autoimmune and rheumatoid disorders. In addition, if iron therapy (oral or intravenous) is started, long-term monitoring for hemochromatosis is necessary.

In Caucasian and North American population the prevalence of RLS ranges from 5% to 10%.[32] In 2005 the REST study showed that only a part of the general population (almost 3% of the subjects enrolled in 5 European countries and in the United States) was affected by severe RLS symptoms occurring more than 2 days per week.[39] In these subjects RLS symptoms impair nocturnal rest, causing difficulties in falling asleep and frequent nocturnal awakenings. Thus, these patients may complain of tiredness and daytime sleepiness, and their family and social lives may be adversely affected.[39] Some subjects report sensory discomfort also when sitting or lying down for a prolonged period during the day. A compromised quality of life (QoL) and an abnormal psychological status are common consequences of severe RLS.[40,41] In addition, recent studies showed that RLS is able to induce cognitive dysfunction[42] and to increase the risk of cardiovascular disease.[43]

In order to detect patients affected by a severe form of RLS, physicians should focus their attention on 3 different features of the sleep disorder: intensity, frequency and consequences (sleep quality, daytime tiredness, mood and quality of life) of RLS symptoms. A recent paper by Happe et al showed that the desire for treatment among patients is determined by a previously known RLS diagnosis, daily symptoms and poor sleep.[44] Unfortunately, the validated scales measuring intensity of RLS symptoms are able to assess only specific characteristics of RLS, for example, the John Hopkins Restless Legs Severity Scale addresses when

RLS symptoms occur over 24 hours, while the RLS-6 scales evaluate the severity of RLS symptoms during different time periods of the day. The International RLS Rating Scale (IRLS) seems to cover more appropriately the clinical spectrum of RLS, it has some limitations, being prone to a placebo effect (see section "Management of RLS with rotigotine") and only partially evaluating RLS consequences on QoL.

Patients with a severe form of RLS require a therapeutic approach. Non-pharmacological treatment, based on physical exercise, sleep hygiene and lifestyle interventions, seems to be useful, but randomized controlled studies are lacking. However, many pharmacological trials on RLS have been performed. On the basis of this increasing scientific literature, several evidence-based reviews have been recently carried out and practice recommendations proposed.[45–51] Differently from evidence-based reviews that mention specific drugs and specific dosages for RLS, practice recommendations recognize levodopa and dopamine agonists as the preferred first-line treatments for RLS.

Both ergoline and non-ergoline dopamine agonists were able to control RLS symptomatology.[50] Since several cases of pleural, pericardial and retroperitoneal fibrosis, and of valvular heart disease have been reported in patients treated with ergot-derived compounds for Parkinson's disease, the most common pharmacological approach to RLS is represented by non-ergoline dopamine agonists.[52,53]

Some patients treated with dopaminergic agents for RLS may report a worsening of their clinical symptoms, a condition known as augmentation. Augmentation is characterized by: (i) an earlier time of symptom onset in the evening or in the afternoon; (ii) a shorter latency to symptom onset when the patient is at rest; (iii) an increase in the intensity of RLS symptoms; iv) a shortening of the period of relief after administration; (v) an expansion of symptoms to previously unaffected body parts.[54] To date, only 2 head to head trials have compared the rate of augmentation under levodopa and dopamine agonists (pergolide and cabergoline). In both studies, the presence of augmentation was more common using levodopa than dopamine agonists.[55,56] On the basis of these results, dopamine agonists are preferred to treat RLS.

The first part of this paper is focused on the diagnostic criteria and differential diagnosis of RLS, while in the second part we review the chemical and clinical characteristics of rotigotine in the management of RLS.

Diagnosis of RLS

Diagnosis of RLS is clinical and based on the characteristics of the sleep-related movement disorder. These characteristics may be summarized in 3 main components: i) sensory, ii) motor, and iii) circadian.

Sensory component

Patients with RLS may report uncomfortable and unpleasant sensations in their legs. Several terms ("creeping", "crawling", "tingling", "cramping", "stubbing", "tension", "pulling", "itching", "burning", "electric current-like", "pain"), often bizarre ("like water flowing", "like worms or bugs crawling under the skin", "Elvis legs", "soda bubbling in the veins"), are used by sufferers to describe their RLS symptoms. However, several RLS patients may be affected by an urge to move their limbs not associated with sensory discomfort or, sometimes, they report being unable to separate out the motor restlessness from their disagreeable sensations.[2] In nearly all RLS patients the sensory component is reported as "deep" and involves both legs. Apart from the legs, also the arms, and less frequently the trunk and face, may be involved with RLS symptoms.[57–63]

Motor component

The urge to move, associated or not with the unpleasant sensations, appears when RLS patients are at rest and is relieved by movement. Thus, sensory and motor components of RLS show a strong relationship. This link can be explained by the role of movement in modulating sensory perceptions.[64] Since rest and immobility can induce the unpleasant sensations in RLS sufferers, Montplaisir et al developed a neurophysiological test, the Suggested Immobilization Test (SIT), in order to help physicians diagnose the sleep disorder. During a 60-minute period the subject is asked to remain in bed with legs outstretched and eyes opened.[65] Compared with normal subjects, RLS patients experience a significantly higher discomfort as estimated by means of a visual analog scale.[66] In order to relieve the sensory component, RLS patients perform several motor patterns, such as turning in bed, stretching, massaging or rubbing the lower limbs, walking around the bedroom, having a warm or cold bath.

In addition, as part of the motor component, RLS patients present involuntary, stereotyped and periodic movements of the lower extremities, known as periodic limb movements (PLM).[67] PLM are characterized by the extension of the big toe with flexion of the ankle, knee and sometimes the hip. These movements can be detected both during sleep and while awake (PLMS and PLMW). Although PLM have a high sensitivity (more than 85% of people with RLS presenting them),[67] they show a low specificity for RLS. In fact, PLM have been described in patients with several other sleep disorders, such

as obstructive sleep apnea syndrome, narcolepsy and REM behavior disorder, and also in the elderly, as a normal variant. PLM detection is based on neurophysiological techniques, usually on polysomnography. In order to be included into a PLM sequence, each limb movement has to last between 0.5 and 5 seconds during sleep and between 0.5 and 10 seconds during wakefulness, recur with a periodicity of 5 to 90 seconds (generally 20–40 seconds) and occur in a series of 4 or more similar movements.[68] PLMS/h (number of leg movements events occurring during sleep that meet PLM criteria, divided by the number of hours of sleep with leg movement recording) and PLMW/h (number of leg movements events occurring during wakefulness that meet PLM criteria, divided by the number of hours of wakefulness with leg movement recording) are the two measures used to assess the severity of PLM. Since PLMS are often related to EEG arousal, the PLM-arousal index (number of leg movements events occurring during sleep that meet PLM criteria and have an associated arousal divided by the number of hours of sleep with leg movement and arousal recording) is scored as well. Due to the fact that several healthy patients without sleep disorders show a PLMS/h above 10,[69] the ICSD-2 suggests that only indexes $\geq$15 should be considered as pathological among adults.[1] During SIT, RLS patients demonstrate a greater number of leg movements, which fulfil criteria for PLMW, compared healthy controls.[70]

Circadian component

In RLS patients the unpleasant sensations and PLM show a characteristic circadian pattern across the 24 hours, with a maximum from 23:00 to 03:00 and a minimum between 09:00 and 14:00.[71–73] This circadian pattern is opposite to the temperature profile, whereas it is in concordance with the melatonin one.[72,73] A recent study attempted to dissociate the effects of immobility duration during SIT from those of intrinsic nycthemeral variations on symptoms of RLS. This investigation showed that the worsening of RLS symptoms due to immobility is closely linked to their intrinsic circadian variation.[74] The timing of the core temperature cycle and the circadian profiles of melatonin, prolactin, cortisol, and growth hormone are normal among RLS patients, thus almost excluding a primary circadian rhythm disorder.[71,72,75,76] To date, the exact role of either sleep drive or circadian variation in RLS symptoms is unknown. Similarly, mechanisms (such as circadian variations of serum iron, co-factor of tyrosine-hydroxylase [rate-limiting enzyme in the production of dopamine], and dopamine itself) involved in the circadian component of RLS have been recently hypothesized, but these suggestions must be confirmed by further future experiments.[77,78]

In 1995 the International RLS Study Group assembled the main components of RLS into 4 diagnostic criteria that were updated in 2003. Besides the essential criteria, the International RLS Study Group detected 3 supportive features: (i) a positive family history for RLS; (ii) a good response to dopaminergic therapy; (iii) the presence of PLM), and 3 associated features (i) a chronic clinical course of RLS; (ii) the disturbance of sleep onset and maintenance of sleep; (iii) normal findings on physical and neurological examinations in primary RLS.[2] Physicians may use the supportive features for patients with doubtful symptomatology, while associated features are useful to reinforce a diagnosis of RLS. Table 1 summarizes the essential criteria, and the supportive and associated features of RLS.

Table 1 Diagnostic criteria for RLS (as defined in[2])

Essential criteria

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 previously present)

Supportive features

1. Positive family history (40%–60% in patients with primary RLS; 12%–13% in patients with secondary RLS)[16]
2. Positive response to dopaminergic therapy (80%–90% after a single dose of 100/25 levodopa/benserazide)[100]
3. Periodic limb movements (during wakefulness or sleep) (Observed in 80%–85% of RLS patients)[67]

Associated features

1. Natural clinical course
2. Sleep disturbance
3. Medical evaluation/physical examination

Differential diagnosis of RLS

Several clinical conditions can mimic RLS.[79] In a large multicenter study performed in a primary care population (the REST primary care study), the authors noticed that only a few patients (52/209 or 24.9%), who satisfied all the essential criteria for RLS reporting symptoms at least twice-weekly with moderate or severe impact on QoL, were correctly diagnosed by their physicians. Varicose veins/venous disorder, back/spinal damage or problem, diabetic neuropathy, depression, myalgia and neuropathy/radiculopathy were the other most common diagnoses.[80] These data demonstrate that the sensitivity of the essential criteria for RLS is lower than 100%. False negative diagnosis of RLS is frequent when the examiner is not familiar with this sleep disorder and, consequently, does not understand the criteria correctly. A higher awareness of RLS is needed among primary care physicians. On the other hand, an erroneous diagnosis of RLS is likely when other conditions mimicking the sleep disorder are present. In fact, several disorders can apparently fulfil all 4 essential criteria for RLS; thus an accurate patient history and physical evaluation is mandatory in order to increase the specificity of RLS diagnosis.

Bearing in mind the 3 main components of RLS, clinical conditions mimicking the sleep disorder can be distinguished in 2 main groups: (i) disorders characterized by motor restlessness or by an abnormal motor pattern at sleep onset or during sleep and (ii) disorders able to cause leg pains or discomfort. Table 2 summarizes these disturbances, emphasizing their discriminative features that are useful in differentiating them from RLS.

Disorders characterized by motor restlessness or by an abnormal motor pattern at sleep onset or during sleep

Neuroleptic-induced akathisia

Patients treated for a long time with neuroleptics may present an inner restlessness involving the whole body, not associated with sensory discomfort. In order to satisfy

Table 2 Differential diagnosis of RLS

Disorders characterized by motor restlessness or by an abnormal motor pattern at sleep onset or during sleep		
Disorder	**General features**	**Discriminating features**
Neuroleptic-induced akathisia	EC1 (only restlessness), EC2	EC1 (no unpleasant sensations), EC3 (often not effective; whole body-rocking movements or marching in place), EC4. SF3 (infrequent). Abuse of neuroleptics
Hypotensive akathisia	EC1, EC2 (only while sitting), EC3	EC2 (none while lying down), EC4. Signs of orthostatic hypotension
Restlessness with volitional movements	EC1 (only restlessness)	EC1 (no unpleasant sensations). SF2. Signs of anxiety
Hypnagogic jerks	EC4. AF2 (if very severe)	EC1, EC2, EC3. SF3
Propriospinal myoclonus	EC4. AF2	EC1, EC2, EC3. SF2
Periodic limb movements disorder	EC4. SF2, SF3. AF2	EC1, EC2, EC3
Disorders able to cause leg pains or discomfort		
Nocturnal leg cramps	EC1 (painful sensations associated with muscular contraction), EC2, EC3 (stretching), EC4	EC1 (no restlessness). SF2, SF3
Painful legs and moving toes	EC1 (painful sensations)	EC3 (often no effective), EC4
Positional discomfort	EC1, EC2, EC3	EC4
Meralgia paresthetica	EC1, EC2, EC3	EC4
Peripheral neuropathy	EC1 (painful sensations), EC2	EC1 (no restlessness), EC3, EC4. SF2. AF3
Myelopathy and radiculopathy	EC1, EC2, EC3	EC1 (no restlessness), EC4. SF2. AF3
Vascular or neurogenic claudication	EC1	EC1 (no restlessness), EC2, EC3, EC4. SF2. AF3
Venous disorders	EC1, EC2, EC3	EC2 (especially while standing up), EC4. SF2. AF3
Vesper's curse	EC1 (pain and paresthesias), EC4	EC1 (no restlessness). SF2. AF3

Abbreviations: EC, essential criteria; SF, supported features; AF, associated features (as defined in[2]).
The number following each acronym refers to the corresponding criterion.

their urge to move, these subjects perform body-rocking movements or start marching in place. Sometimes, these motor patterns are not effective in improving restlessness. Differently from RLS, the neuroleptic-induced akathisia does not show a circadian pattern and has a significantly lower rate of PLM.

Hypotensive akathisia

A clinical condition characterized by restlessness involving lower extremities and occurring in the sitting position. This disorder is due to autonomic failure, and thus can be associated with orthostatic hypotension. Patients develop the adaptive habit of restless leg movements in order to reduce drops in blood pressure while sitting. In the lying down position clinical symptoms disappear. Symptoms of hypotensive akathisia do not worsen in the evening or at night.

Restlessness with volitional movements

Repetitive volitional movements in the lower extremities may occur in patients with anxiety and/or insomnia. These motor activities are not associated with sensory discomfort and are treated with benzodiazepines.

Hypnagogic jerks

Sudden physiologic jerks of all or part of the body that occur during the transition between wake and sleep. Occasionally these myoclonic activations are so frequent and severe that affected patients report difficulty in sleep onset. Associated sensory discomfort and PLM are not present.

Propriospinal myoclonus

Massive symmetric jerks not associated with sensory discomfort, arising from axial muscles and spreading rostrally and caudally. These myoclonic movements are spinal-cord-mediated and may be related to spinal damage. They appear during relaxation and result in severe sleep-onset insomnia. Benzodiazepines and anticonvulsants are used as pharmacological therapy.

Periodic limb movements disorder

Sleep-related motor disorder characterized by the repetitive occurrence of PLM during sleep and able to cause fragmented nocturnal rest or excessive daytime sleepiness. Differently from individuals suffering from PLM associated to RLS, these patients do not complain of restlessness or disagreeable sensations in the legs. However, similarly to RLS, dopaminergic agents are effective in decreasing PLM number.

Disorders able to cause legs pain or discomfort

Nocturnal leg cramps

Painful sensations due to prolonged muscular contractions appearing during sleep and involving specific muscles, generally the calf ones. Motor restlessness and PLM are not present. Differently from RLS patients, subjects with leg cramps present a palpable tightening of leg muscles. Leg cramps do not respond to dopaminergic agents and are alleviated by stretching and not by movement.

Painful legs and moving toes

Uncommon syndrome in which patients refer to painful sensations in the feet associated with slow, involuntary and repetitive toe movements. These movements often do not improve the sensory discomfort and do not show a circadian pattern.

Positional discomfort

This comes from prolonged sitting or lying down positions. A simple change of position relieves the sensory discomfort. A circadian pattern is absent.

Meralgia paresthetica

Postural positions during sitting and lying down may cause a compression of lateral femoral cutaneous nerve with paresthesia. As positional discomfort, a change of position is able to improve the clinical symptomatology and a circadian pattern of the disturbance is lacking.

Peripheral neuropathy

Patients with peripheral neuropathy frequently report painful sensations, without restlessness, in the upper and lower extremities. As RLS, these sensations may impair at rest, but do not improve with sustained movements and rarely worsen in the evening or at night. Peripheral neuropathy does not respond to dopaminergic therapy. Signs of polyneuropathy should be detected by means of a neurological examination.

Myelopathy and radiculopathy

Spinal or radicular damages may reveal themselves as dysesthesia and painful sensations, but no restlessness, in the lower extremities. These complaints frequently occur in the sitting or lying down position and are improved by movement. Differently from RLS, a circadian pattern of the clinical symptoms and a positive response to dopaminergic agents are lacking. A physical examination might reveal atrophic changes of musculature with skin abnormalities.

Vascular or neurogenic claudication

Clinical conditions characterized by dysesthesia and painful sensations, but no restlessness, increasing in intensity during leg movements and relieved at rest. These symptoms do not worsen in the evening or at night. Skin alterations are common.

Venous disorders

A sensory discomfort that is impaired at rest, particularly in standing up position, and improved by movement may be due to venous stasis. Differently from RLS, venous disorders do not show a circadian pattern and a positive response to dopaminergics. Skin alterations and edema might be observed during physical examination.

Vesper's curse

An increase in the right atrium filling pressure due to chronic heart failure causes a delay in venous circulation. This clinical condition may lead to an increase in the pressure and enlargement of the lumbar veins with a relative narrowing of the spinal canal and reduced oxygenation. Affected patients report lumbosacral and associated leg pain and paresthesias generally occurring in the afternoon and evening. PLM can be observed. Vesper's curse does not respond to dopaminergic agents. Cardiopulmonary alterations are common and should be detected during physical examination.

Physicians should consider that some clinical conditions able to mimic RLS can also induce secondary forms of RLS. In fact, variants of RLS due to neuroleptic abuse and peripheral neuropathy have been identified. Although systematic studies are lacking, several case-reports show the occurrence of RLS in patients treated for a long time with antipsychotics.[81–85] Pathophysiology of this symptomatic form of RLS should be related to the drug's blocking effects on dopamine receptors. Although both typical and atypical neuroleptics seem to be able to cause the sleep disorder, drugs with less blocking action on D_2 receptor, such as clozapine and quetiapine, might be less dangerous. The association between RLS and peripheral neuropathy was initially described by Ekbom and, subsequently, confirmed by many studies.[86–93] These studies revealed that the axonal-sensory and the small-fiber polyneuropathies are the most common causes of RLS.[89–93] An imbalanced equilibrium in the dorsal horn of the spinal grey matter among the excitatory nociceptive inputs, due to the peripheral neuropathy, and the inhibitory ones descending from the diencephalon might explain the occurrence of RLS in the course of peripheral neuropathy.[33] Differently from primary RLS, patients affected by RLS due to polyneuropathy identify the sensory discomfort in the legs as painful sensations.[33,92]

Management of RLS with rotigotine

Rotigotine is a non-ergoline dopamine agonist with similar actions to those of bromocriptine, but in contrast to bromocriptine (a dopamine D_2-agonist) it also has agonist properties at D_1 and D_3 receptors.

Chemistry

The chemical name of rotigotine is S-(-)-2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin hydrocloryde. The empirical formula is $C_{19}H_{25}NOS$. The molecular weight is 315.48 Da.

Pharmacodynamics

Rotigotine demonstrates D_1, D_2 and D_3 agonist activity, with an almost 15-fold higher affinity for the D_2 receptor than for the D_1 receptor. Rotigotine improved motor deficits in animal models of Parkinson's disease, including when administered transdermally. The efficacy of rotigotine in controlling RLS symptomatology might be due to the fact that this compound is able to restore dopaminergic transmission. Rotigotine has also α_2 adrenergic receptor antagonistic and 5-HT_{1a} agonistic activity.

Pharmacokinetics and metabolism

Rotigotine is given as transdermal patches because of a low oral bioavailability due to an extensive first-pass effect. This transdermal delivery system bypasses the gut wall and the hepatic circulation, and provides stable plasma levels. On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 mg/cm^2), independently of patch size. When single doses of 40 cm^2 systems are applied to the trunk, there is an average lag time of approximately 3 hours until the drug is detected in plasma (range 1–8 hours). T_{min} occurs most commonly between 0 and 7 hours post dose. T_{max} typically occurs between 15 to 18 hours post dose but can occur from 4 to 27 hours post dose. After removal of the patch, plasma levels decrease and have a terminal half-life of 5 to 7 hours. Rotigotine displays dose-proportionality over a daily dose range of 2 mg/24 hours to 8 mg/24 hours. In the clinical studies of rotigotine effectiveness, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm) and the mean measured plasma concentrations of rotigotine were stable over the 6 months of maintenance treatment. In healthy subjects, steady-state plasma concentrations of rotigotine were achieved within 2 to 3 days of daily dosing. Relative bioavailability for the different application sites at steady-state was evaluated in subjects with Parkinson's disease.

Differences in bioavailability ranged from less than 1% (abdomen vs hip) to 64% (shoulder vs thigh), with shoulder application showing higher bioavailability. As rotigotine is administered transdermally, food does not affect absorption of the product, so it can be administered without regard to the timing of meals. The weight normalized apparent volume of distribution (Vd/F) in humans is approximately 84 L/kg after repeated dose administration. The binding of rotigotine to human plasma proteins is approximately 92% in vitro and 89.5% in vivo. Rotigotine is extensively metabolized by conjugation and N-dealkylation. Rotigotine is primarily excreted in urine (~71%) as inactive conjugates of the parent compound and N-desalkyl metabolites. A small amount of unconjugated rotigotine is renally eliminated (<1% of the absorbed dose).

Administration

Patch sizes used in clinical trials in patients with idiopathic RLS were 2.5 cm^2 (rotigotine dosage 0.5 mg/24 hours; total drug content 1.125 mg), 5 cm^2 (1 mg/24 hours; 2.25 mg), 10 cm^2 (2 mg/24 hours; 4.5 mg), 15 cm^2 (3 mg/24 hours; 6.75 mg), and 20 cm^2 (4 mg/24 hours; 9.0 mg). Patches are applied once daily and should be replaced every 24 hours with the new patch applied to a different site. When given for idiopathic RLS, the initial rotigotine dose is 0.5 mg/24 hours (patch size 2.5 cm^2), increased in weekly steps of 2 mg, if necessary. A maximum dose of 4 mg/24 hours (patch size 20 cm^2) is used to treat RLS symptoms. Higher dosages (until 16 mg/24 hours) are used in patients with early or advanced Parkinson's disease. Treatment with rotigotine should be withdrawn gradually; the daily dose should be reduced in steps of 2 mg every other day until complete withdrawal is achieved. An abrupt withdrawal of the drug might lead to a syndrome resembling neuroleptic malignant syndrome or akinetic crises.

Special population

Hepatic insufficiency

The effect of impaired hepatic function on the pharmacokinetics of rotigotine has been studied in subjects with moderate impairment of hepatic function. There were no relevant changes in rotigotine plasma concentrations. No dose adjustment is necessary in subjects with moderate impairment of hepatic function. No information is available on subjects with severe impairment of hepatic function; however, in these patients rotigotine should be used with caution.

Renal failure

The effect of renal function on rotigotine pharmacokinetics has been studied in subjects with mild to severe impairment of renal function including subjects requiring dialysis compared to healthy subjects. There were no relevant changes in rotigotine plasma concentrations. In subjects with severe renal impairment not on dialysis (ie, creatinine clearance 15 to <30 mL/min), exposure to rotigotine conjugates was doubled. Rotigotine concentrations did not decrease in patients with renal failure undergoing hemodialysis and the drug was not observed in the dialysis fluid.

Geriatric patients

Plasma concentrations of rotigotine in patients 65 to 80 years of age were similar to those in younger patients, approximately 40 to 64 years of age. Although not studied, exposures in older subjects (>80 years) may be higher due to skin changes with aging.

Pediatric patients

The pharmacokinetics of rotigotine in subjects below the age of 18 years have not been established.

Pregnant and breastfeeding women

There are no adequate data from the use of rotigotine in pregnant women. Animal studies do not indicate any teratogenic effects in rats and rabbits, but embryo toxicity was observed in rats and mice at maternotoxic doses. The potential risk for humans is unknown. Rotigotine should not be used during pregnancy. Rotigotine decreases prolactin secretion in humans and could potentially inhibit lactation. Studies in rats have shown that rotigotine and/or its metabolite(s) is excreted in breast milk. It is not known whether rotigotine is excreted in human breast milk. Because of the possibility that rotigotine may be excreted in human milk, and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Clinical efficacy, safety and tolerability

The evidence of the efficacy of rotigotine in treating patients with Parkinson's disease has led to the use of the drug in RLS patients. The first pilot study to show proof-of-principle of rotigotine therapy in RLS was conducted by Stiasny-Kolster et al in 2004.[94] Patients affected by moderate to severe idiopathic RLS and who had responded previously to levodopa were recruited in the trial. Three fixed doses of rotigotine (1.125 mg, 2.25 mg, and 4.5 mg/daily) were compared with placebo over a period of 1 week. No dose titration was performed. The primary efficacy measure was the total score on the IRLS. Secondary endpoints were the RLS-6 scales

and the Clinical Global Impression (CGI). A dose-response relationship was observed: RLS severity improved by 10.5 (1.125 mg/die), 12.3 (2.25 mg/die), and 15.7 points (4.5 mg/die) in the IRLS compared with placebo (8 points). Higher improvements in the RLS-6 scales were also observed in patients treated with rotigotine compared with the placebo group in the severity of symptoms at bedtime or during the night. However, no differences were detected in the RLS-6 quality of sleep and tiredness at daytime. Adverse events were rare and mild. The most common adverse event was the application site reaction seen in 26.5% of patients treated with rotigotine and in 28.6% of patients treated with placebo. Headache was the second most common side effect (22.4% of patients receiving rotigotine vs 7.1% of patients receiving placebo). Overall adverse events were more frequent in the two higher rotigotine dose groups (2.25 mg and 4.5 mg).

A longer trial with higher doses of rotigotine was conducted in 2007 by Oertel et al in order to better investigate the benefits of rotigotine treatment in patients with idiopathic RLS.[95] This was a randomized, multi-center, double-blind, placebo controlled 6-week trial using rotigotine patches with fixed doses of 0.5 mg/24 hours (1.125 mg), 1 mg/24 hours (2.25 mg), and 2 mg/24 hours (4.5 mg), 3 mg/24 hours (6.75 mg), 4 mg/24 hours (9.0 mg). Study population consisted of severely affected patients with a long history of RLS, who had been previously treated with dopaminergic drugs. Patients were randomly assigned to one of the six treatment groups and no drug dosage variations were allowed. Change in IRLS total score from baseline to the end of treatment was the primary efficacy variable. The study showed a dose-response relationship in the dose range 0.5 mg/24 hours and 3 mg/24 hours. The 0.5 mg/24 hours dose was not statistically significantly superior to placebo. The higher dosage (4 mg/24 hours) showed a minor improvement in the IRLS total score compared to 3 mg/24 hours. However, no differences were seen between the effects of 1 mg/24 hours and 2 mg/24 hours. Other outcomes variables were the CGI, the RLS-6 scales and the QoL. Improvements in the CGI showed a similar dose-response relationship as seen with the IRLS. The RLS-6 scales showed an improvement of RLS symptoms at bedtime and during the night and a reduced tiredness during the day. As a consequence, the QoL improved in all treatment groups. The trial demonstrated how rotigotine improves RLS symptoms in a therapeutic window between 1 mg/24 hours and 3 mg/24 hours. Despite the large placebo effect (responder rate of 42%) treatment with rotigotine in the therapeutic window cited above was demonstrated to be statistically superior in reducing RLS symptoms. Higher doses (4 mg/24 hours) have not demonstrated an additional benefit and led to more adverse events. Adverse events were seen in 62% of patients receiving rotigotine and in 45.5% of patients in the placebo group. Application site reaction was the most common side effect seen in 17.5% of patients receiving rotigotine and in 1.8% of patients receiving placebo. Serious adverse events were reported in 6 patients.

Of the 310 patients who finished this trial, 295 patients with a mean IRLS score of 27.8 ± 5.9 were included in an open label trial that observed long term (1 year) safety and tolerability of rotigotine.[96] Patients were divided into 2 groups: those whose IRLS showed an improvement of at least 50% stopped treatment with rotigotine but could restart treatment by entering the trial if the clinical condition worsened; those who instead had shown minor improvements in the pervious trial entered immediately the second trial. Patients were excluded if severe adverse events had occurred or if they had not been compliant during the double blind study. Drug titration started with 0.5 mg/24 hours; the dose could be increased up to a maximum dose of 4 mg/24 hours. The mean daily dose after 12 months was 2.8 ± 1.2 mg/24 hours. Increases of the initial dose occurred in 51.7% of patients: once in 27.2%, twice in 16.6%, 3–5 times in 7.9%. Dose adjustments occurred in the first month of therapy but afterwards doses remained stable. Outcome parameters included the IRLS sum score, the RLS-6 scales, the CGI and the QoL-RLS. After 12 months all these efficacy parameters improved. A mean change in the IRLS total score of 17.4 was observed; 68% of the patients showed an improvement of at least 50% in the IRLS total score. For the RLS-6 severity scale, relief from symptoms at bedtime, during the night, during daytime when patients were at rest and reduced tiredness during the day were observed. This led to an improved QoL. Rotigotine was well tolerated, as only minor adverse events were observed. Application-site reaction occurred in 40% of patients but it was generally mild and could be resolved after changing the application site. Nausea and fatigue were the second most common side effects seen in 9.5% and 6.4% of patients, respectively.

Another trial was conducted in 2008 by Trenkwalder et al.[97] The effects of rotigotine at the lowest levels of effectiveness were studied over a period of 6 months. The study population consisted of patients affected by severe or very severe idiopathic RLS (mean IRLS sum score 28.1 ± 6.1), the majority of whom had been previously treated with dopaminergic drugs (71.1%). Patients were randomly assigned to receive placebo or rotigotine 1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours. Efficacy outcomes were: the IRLS sum score,

the CGI, the RLS-6 scales, the QoL-RLS and the Medical Outcomes Study (MOS) sleep scale. At the end of the trial significant improvements in the IRLS sum score and in the CGI were observed for all rotigotine dosages compared with placebo. The improvement observed showed a dose-response relationship, with the higher effects seen for the rotigotine 3 mg/24 hours. Also the QoL improved with a dose-response relationship. Adverse events were seen in 77.7% of patients receiving rotigotine and in 55% of patients receiving placebo. As seen in previous trials, the most common adverse effect was application-site drug reaction (42.5% of patients receiving rotigotine).

Only 2 of the 4 trials evaluating the efficacy of rotigotine transdermal delivery system in idiopathic RLS assessed the presence or severity of augmentation. Although standardized criteria to detect augmentation were not applied, Oertel et al did not report any patient with this adverse event.[96] Trenkwalder et al observed similar scores at the Augmentation Severity Rating Scale – 4 items between placebo and each dose of rotigotine.[97]

Treatment of RLS with dopamine agonists has been infrequently associated with sudden and unintended sleep attacks.[98] Because sleep attacks under rotigotine treatment are infrequent and moderate in intensity, no patients with this adverse event discontinued the trial or changed the drug dose.[94–97]

Table 3 shows the main characteristics of the 4 trials on rotigotine in idiopathic RLS. The prevalence of the most frequent adverse events due to rotigotine and placebo in the 4 trials is reported in Table 4.

As reported in Table 3, RLS patients recruited in trials on rotigotine showed a large placebo effect. Elevated placebo responder rates were also observed in almost all drug trials conducted in RLS. The IRLS, which is considered the gold standard scale to assess RLS severity, is particularly prone to this condition. A possible explanation is that this tool includes items covering aspects that are not highly

Table 3 Main characteristics of the four trials on rotigotine in idiopathic RLS (IRLS)

Trial	Stiasny-Kolster et al 2004[94] Randomized, double-blind, placebo-controlled, multi-center trial	Oertel et al 2008[95] Randomized, double-blind, placebo-controlled, multi-center trial	Oertel et al 2008[96] Open label, single arm, multi-center trial	Trenkwalder et al 2008[97] Randomized, double-blind, placebo-controlled trial
Study duration	1 week	6 weeks	1 year	6 months
Number of pts (ITT population)	63	333	295	447
Age of pts	58.3 ± 8.8	58.4 ± 10.3	58.0 ± 10.0	57.7 ± 11.1
Sex, female (%)	63.5	67.3	66.0	71.1
Duration of RLS (yr)	10.5 ± 9.5	11.0 (median)	11.0 (median)	n.a.
Previous dopaminergic treatment (%)	85.7 (levodopa) 15.9 (DA)	72.4 (levodopa) 40.5 (DA)	72.4 (levodopa) 40.5 (DA)	71.1
Previously untreated (%)	12.7	19.2	19.2	27.9
IRLS severity	25.9 ± 5.1 (range 16–38)	27.9 ± 6.0	27.8 ± 5.9	28.1 ± 6.1 (range 15–40)
Daily rotigotine dosage	0.5 mg/24 h 1 mg/24 h 2 mg/24 h	0.5 mg/24 h 1 mg/24 h 2 mg/24 h 3 mg/24 h 4 mg/24 h	Mean daily dose 2.8 ± 1.2 mg/24 h	1 mg/24 h 2 mg/24 h 3 mg/24 h
Primary efficacy measure	IRLS	IRLS	IRLS	IRLS
Secondary endpoints	RLS-6, CGI	RLS-6, CGI, QoL-RLS	RLS-6, CGI, QoL-RLS	RLS-6, CGI, QoL-RLS, MOS
Mean change from baseline in the IRLS sum score	10.5 points[a] 12.3 points[b] 15.7 points[c] 8 points[f]	10.6 points[a] 15.1 points[b] 15.7 points[c] 17.5 points[d] 14.8 points[e] 9.2 points[f]	Mean change of 17.4 points	13.7 points[b] 16.2 points[c] 16.8 points[d] 8.6 points[f]

Mean IRLS change for: [a]0.5 mg/24 hours; [b]1 mg/24 hours; [c]2 mg/24 hours; [d]3 mg/24 hours; [e]4 mg/24 hours; [f]placebo.

specific for RLS, such as sleep quality, daytime tiredness, mood and quality of life.[99]

Regulatory affairs

Rotigotine was approved by the FDA for treatment of early Parkinson's disease and by the EMEA for treatment of all stages of Parkinson's disease. The drug has been recommended for approval by the EMEA and is under review by the FDA for the treatment of moderate to severe idiopathic RLS. Recently, rotigotine has been recalled because of the formation of drug crystals in the patches. Due to crystal formation, in these patches rotigotine is less available to be absorbed through the skin, thus the efficacy of the affected product may vary.

Discussion and Conclusion

RLS is one of the most common neurological disorders and, if severe, it may affect the patient's life, impairing physical and mental health. Although diagnosis of RLS is clinical and based on internationally recognized clinical criteria, it is not always easy, in particular when physicians are not familiar with this sleep disorder. In order to increase the sensibility and specificity of RLS diagnosis, physicians should perform a careful patient history and then a meticulous physical and neurological examination.

Patients affected by severe and frequent symptoms of RLS should receive pharmacological treatment. In subjects with RLS associated with iron deficiency (serum ferritin levels lower than 50 μg/L) an attempt with replacement treatment is mandatory. Intravenous iron is likely more effective in improving RLS symptoms than oral iron. The adverse events due to oral (eg, gastrointestinal disturbances) and intravenous (eg, anaphylaxis) iron, and a possible risk for hemochromatosis should be carefully considered by physicians.

Patients affected by idiopathic RLS should be treated with dopaminergic agents (non-ergoline dopamine agonists and levodopa), that are considered to be first-line therapy.

Table 4 Prevalence of the most frequent adverse events due to rotigotine and placebo in the four trials

	Stiasny-Kolster et al 2004[94]		Oertel et al 2008[95]			Oertel et al 2008[96]	Trenkwalder et al 2008[97]	
	Rotigotine	Placebo	Rotigotine		Placebo	Rotigotine	Rotigotine	Placebo
Any adverse event (%)	n.a.	n.a.	64.7[a] 48.4[b] 57.1[c]	75.4[d] 64.3[e]	45.5	79.0	73[b] 80[c] 80[d]	55
Any serious adverse event (%)	n.a.	n.a.	2.0[a] 1.6[b] 0.0[c]	3.1[d] 0.0[e]	1.8	7.8	6.0[b] 4.0[c] 11.0[d]	4.0
Application site reaction (%)	17.6[a] 38.5[b] 26.3[c]	28.6	9.8[a] 15.6[b] 16.3[c]	20.0[d] 25.0[e]	1.8	40.0	35.0[b] 41.0[c] 52.0[d]	2.0
Headache (%)	11.8[a] 38.5[b] 21.1[c]	7.1	11.8[a] 7.8[b] 2.0[c]	4.6[d] 12.5[d]	7.3	4.1	10.0[b] 13.0[c] 16.0[d]	7.0
Nausea (%)	0.0[a] 7.7[b] 5.3[c]	14.3	5.9[a] 9.4[b] 6.1[c]	24.6[d] 23.2[e]	9.1	9.5	9.0[b] 21.0[c] 18.0[d]	3.0
Fatigue (%)	0.0[a] 0.0[b] 10.5[c]	0.0	3.9[a] 4.7[b] 6.1[c]	10.8[d] 7.1[e]	9.1	6.4	7.0[b] 15.0[c] 11.0[d]	9.0
Pruritus (%)	5.9[a] 15.4[b] 0.0[c]	7.1	5.9[a] 3.1[b] 0.0[c]	10.8[d] 3.6[e]	1.8	n.a.	n.a.	n.a.
Insomnia (%)	0.0[a] 7.7[b] 5.3[c]	7.1	n.a.		n.a.	3.7	0.0[b] 0.0[c] 7.0[d]	3.0
Hyperhidrosis (%)	0.0[a] 0.0[b] 10.5[c]	0.0	n.a.		n.a.	n.a.	5.0[b] 6.0[c] 4.0[d]	3.0

Prevalence of adverse events for: [a]0.5 mg/24 hours; [b]1 mg/24 hours; [c]2 mg/24 hours; [d]3 mg/24 hours; [e]4 mg/24 hours.

In subjects with RLS not complaining of daytime symptoms, oral non-ergoline dopamine agonists or levodopa should be preferred. These compounds are able to control RLS symptomatology also when present during daytime, but, because of their short half-life, patients should take the medications many times during the day. This condition might significantly reduce treatment compliance. Thus, we think that RLS patients complaining of daytime symptoms might benefit from a medication with continuous delivery, such as transdermal patches of rotigotine. However, the effectiveness and safety of dopaminergic compounds administered via different routes in treating RLS might be dissimilar. Comparative trials are needed.

Based on clinical trails and our experience, rotigotine seems to control the symptomatology effectively and to be well tolerated when used in patients with this sleep disorder. In particular, RLS symptoms are generally improved by rotigotine in a therapeutic window between 1 mg/24 hours and 3 mg/24 hours. If necessary, a higher dose of 4 mg/24 hours should be administered. Application-site reactions, headache and nausea may be reported, but these adverse events are generally moderate in intensity and patients do not need to stop their treatment. Although based on a few clinical trials, augmentation and sleep attacks do not appear to be common adverse effects of rotigotine when used for RLS patients.

If augmentation occurs under rotigotine or another dopamine agonist, physicians should reduce or split the dosage. Alternatively, a therapeutic change with opioids/gabapentin or a combination therapy administering very low doses of dopamine agonists with opioids/gabapentin should be considered. For the occurrence of augmentation under levodopa at lower range of recommended doses, the physician should try to split the medication into 2 doses, 1 given in the afternoon and 1 in the evening. Alternatively a longer-acting dopaminergic agent should be administered. To treat augmentation during higher dosages of levodopa, the physician should switch to dopamine agonists.

Disclosures

The authors report no conflicts of interest.

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