

The status of rotigotine as a safe and effective alternative in the treatment of restless legs syndrome

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Abstract: Restless legs syndrome (RLS) is characterized by an urge to move the legs that occurs mainly with inactivity, and it is relieved by movement and is usually worse by the end of the day. It is highly prevalent, affecting 1.9% to 4.5% of the population, and although its etiology is uncertain, genetic factors seem to be involved. When symptoms are severe enough to warrant chronic therapy, dopamine receptor agonists are to be considered for initial treatment. Rotigotine, the most recently developed drug in this category, is the only one available for transdermal delivery in RLS. It was initially designed for the treatment of Parkinson's disease. The US Food and Drug Administration approved its use in cases of moderate to severe RLS in April 2012. Its efficacy has been well established in randomized placebo-controlled trials, as it appears to be especially useful in patients with daily symptoms. The most commonly reported side effect is local skin reaction. Complications such as augmentation, somnolence, or compulsive behavior may happen, although they seldom occur. The American Academy of Sleep Medicine clinical practice guideline recommends a "Guideline Level" for rotigotine, and European RLS guidelines provide a "level A" recommendation for short-term therapy; it also was the only dopaminergic agonist considered to be effective for the long-term management of RLS.

Keywords: restless legs syndrome, 2-rotigotine, dopamine receptor agonist

Introduction

Thomas de Quincey, a British writer of the 19th century, and author of "*Confessions of an English-Opium eater*",¹ has described how his life had become miserable after suffering from insomnia. The symptoms he described were consistent with possible restless legs syndrome (RLS), and it was postulated that his opium addiction could have resulted from the need to treat himself.²

RLS was first described by Sir Thomas Willis in 1685,² but awareness of this disease was greatly enhanced following Ekbom's work³ beginning in the 1940s, to which we owe the appellation "restless legs syndrome." The term "Ekbom's disease" has also been used as a credit to his contribution.

RLS is a disorder frequently encountered in the general practitioner's office, but also in neurology, psychiatry, and sleep clinics. It may cause severe distress and has a negative impact on the quality of life of sufferers. Patients report an urge to move their legs, usually accompanied by an unpleasant sensation that is difficult to depict, which is temporarily relieved by movement. It usually emerges at the end of the day, and may compromise sleep.

Different pharmacological interventions have been used to treat this disorder, such as dopaminergic stimulation, or the usage of anticonvulsants or opioids, as De Quincey

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discovered for himself. Rotigotine is the only transdermally delivered dopaminergic agonist available, enabling a continuous release of the drug through a 24-hour period. Here, we will first review RLS and the different components of this disorder, and then we shall ascertain the evidence supporting rotigotine as a potent agent in the treatment of this condition.

Clinical features and diagnosis

RLS is characterized by an urge to move the legs, usually accompanied by an uncomfortable sensation that is at least partially alleviated by movement. It occurs mainly with inactivity and particularly at the end of the day. This sensation is typically difficult to describe by patients, and may be reported as itching, burning, crawling, creeping, or stretching. It is a frequent condition, with as many as 1.9% to 4.5% of the population fulfilling the diagnostic criteria (Table 1).^{4,5} However, it remains an under-diagnosed entity, even when patients report their symptoms to their physician.⁶ In some cases, RLS may be caused by an underlying disease (iron deficiency anemia, end-stage chronic renal disease, peripheral neuropathy), but it is usually an idiopathic disorder for which the etiology is uncertain, although genetic factors are known to be involved.^{7–16}

Quality of life is greatly reduced by RLS, as much as in other chronic diseases like diabetes or depression.^{6,17,18} Prospective data have shown that women with RLS are at higher risk of developing clinical depression.¹⁹ Several cognitive functions might be affected by RLS, including verbal fluency and attention,^{20–22} mostly in patients with moderate to severe disease. RLS also causes a significant economic

burden for patients and society alike, with a mean productivity loss estimated at 1 day per week in RLS sufferers.¹⁷ Many treatments are available, and here we will first review briefly some therapeutic options, and then we will examine the evidence supporting the use of rotigotine in RLS.

Therapeutic options: dopaminergic stimulation

The decision of whether or not to treat RLS is based on severity, frequency, and distress associated with the symptoms. Some individuals with mild, intermittent symptoms may not necessitate any treatment, or only on an occasional basis, while patients suffering from moderate to severe symptoms may require daily therapy. Many authors have provided reviews on the numerous treatment options, and two large consensuses have also provided specific guidelines for treating RLS.^{23–29}

Dopaminergic receptor-stimulating drugs represent the most effective and the most widely prescribed drugs in RLS. These include levodopa and all the dopamine receptor agonists (Table 2). These medications are associated with well-known side effects such as nausea, drowsiness, and dizziness. More bothersome complications include sleep attacks, compulsive behavior, and augmentation, which have been recognized as complications related to dopaminergic therapy for RLS since their first description in 1996 following levodopa–carbidopa usage.³⁰ Augmentation is characterized by a worsening of symptoms after an initial positive response to RLS treatment. It may cause earlier occurrence, with increasing intensity or extension to other body parts. Increasing the doses of the dopaminergic agent

Table 1 Diagnostic criteria of RLS

Essential diagnostic criteria	<ol style="list-style-type: none"> 1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move the legs 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, which 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 clinical features	<p>Family history The prevalence of RLS among first-degree relatives of people with RLS is three to five times greater than people without RLS.</p> <p>Response to therapy Nearly all people with RLS show at least an initial positive therapeutic response to either L-dopa or a dopamine receptor agonist at doses considered to be very low in relation to traditional doses of these medications used for the treatment of Parkinson's disease. This initial response is not, however, universally maintained.</p> <p>Periodic limb movements (during wakefulness or sleep) PLMS occur in at least 85% of people with RLS; however, PLMS also commonly occur in other disorders and in the elderly. In children, PLMS are much less common than in adults.</p>

Abbreviations: RLS, restless legs syndrome; PLMS, periodic limb movements in sleep.

Table 2 Dopaminergic stimulation

Class	Medication	Mechanism	T _{max} (hours)	Half-life (hours)	Comments
Dopamine therapy	Levodopa–carbidopa/ benserazide	Precursor of dopamine	0.5–2	1–3	Absorption decreases when taken with meals
Ergot-derived dopamine receptor agonists	Bromocriptine	D ₂ agonist, partial D ₁ agonist	1–1.5	6–8	Liver metabolism
	Cabergoline	D ₂ selective agonist 5-HT _{2b} agonist	2.5	65	Causes cardiac valvular fibrosis
Nonergot-derived dopamine receptor agonists	Ropinirole	D ₂ /D ₃ agonist	1.5	6	Liver metabolism
	Pramipexole	D ₂ /D ₃ agonist	1–3	10	Largely excreted unchanged in urine
	Rotigotine	D ₃ /D ₂ /D ₁ agonist	14	5–7	Liver metabolism 65%–70% excreted by the kidneys

Abbreviation: T_{max}, time to peak concentration.

should transiently relieve the symptoms, but will eventually lead to further deterioration.³¹

Levodopa

Multiple small clinical trials support the efficacy of levodopa in RLS.²⁴ Its short time to peak concentration makes it suitable for intermittent as-needed treatment. However, a high rate of augmentation (up to 80%), which may be severe (leading to discontinuation in 50% of patients), has been reported with chronic therapy.^{23,30} Because of its short half-life, levodopa may also be associated with a rebound phenomenon, leading to late-night or morning recurrence of symptoms.²⁴ Considering these complications, when daily therapy is needed, other alternatives should be considered.

Ergolic dopamine receptor agonist

Ergot-derived dopamine receptor agonists include bromocriptine and cabergoline. Evidence of the efficacy of bromocriptine is weaker than that of cabergoline. According to a recent meta-analysis,²⁵ the latter medication, presumably because of its longer half-life, yielded superior therapeutic efficacy and offered better daytime relief of symptoms compared to the relatively short-acting non-ergolic oral dopamine agonists. This was associated with a positive impact on quality of life. However, since it has a recognized risk of cardiac valvular fibrosis, it can no longer be advocated for the treatment of RLS.

Nonergolic dopamine receptor agonist

Nonergot-derived dopamine receptor agonists include rotigotine, ropinirole, and pramipexole. They are frequently used as first-line therapy in clinical practice and are potent drugs for alleviating the symptoms of RLS. A recent meta-analysis con-

cluded that the clinical benefit is similar between ropinirole and pramipexole, although no study has compared these drugs in a head-to-head trial. As a newer agent, rotigotine has not been compared to the two latter dopamine receptor agonists. Compared to placebo, transdermal delivery was shown to be associated with better daytime control of symptoms and improved quality of life.²⁶

Therapeutic options: rotigotine

Rotigotine was first approved for use in early-stage Parkinson's disease by the Food and Drug Administration (FDA) in 2007, but was withdrawn from the market in 2008 because of concerns about inconsistent absorption due to drug crystallization. Since then, a rotigotine patch (Neupro®, UCB SA, Brussels, Belgium) was reformulated to prevent crystallization. It was approved again in April 2012 for the treatment of moderate to severe RLS. It was expected that the 24-hour delivery system would have some benefit over the other drugs for relieving diurnal symptoms.

Structure, mode of action, and pharmacokinetics

Rotigotine, or S-(–)-2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin hydrochloride, is a nonergolic dopamine D₃/D₂/D₁ agonist that also has activity on α₂-adrenergic, 5-HT_{1A}, and 5-HT₂ receptors.³² It is a silicone-based transdermal system that releases the drug in a continuous manner over 24 hours.³³ Between 31% and 62% of the total drug content is delivered to the skin, with a high interindividual variability of 54%, but with low variability within individuals (15%).³⁴ The drug is mostly eliminated by renal excretion (65%–70%), with a half-life of 5 to 7 hours, and it is barely detectable 96 hours after removal of the patch.^{35,36}

Clinical studies of rotigotine in RLS

Rotigotine was first assessed in the treatment of Parkinson's disease.^{33,37} Five randomized, placebo-controlled clinical trials evaluated rotigotine in the treatment of RLS (Table 3).

Two small trials have provided significant data concerning clinical efficacy and objective sleep. A 1-week pilot trial published in 2004 showed a positive dose-response, but only the 4.5 mg dose reached superiority against placebo.³⁸

A 2010 4-week polysomnographic study compiled data supporting a significant reduction in periodic limb movement in sleep, a frequently comorbid condition in RLS, altogether with a reduction in RLS motor symptoms.³⁹

Larger clinical trials have led to the approval of rotigotine by the FDA. The first one, published in 2008, consisted of a 6-month randomized, placebo-controlled trial of 458 patients comparing doses ranging from 1 mg/24 hours to 3 mg/24 hours.⁴⁰ It confirmed efficacy both on the International Restless Legs Severity scale (IRLS) and the Clinical

Global Impression scale for all three doses against placebo. Skin reactions were frequent (43%), but severe reactions were seldom seen (1.8%).

Hening et al⁴¹ have published a similar trial in 2010 involving 505 patients randomized either to placebo or to one of four different doses (0.5 mg/day, 1 mg/day, 2 mg/day, or 3 mg/day) with 6 months of follow-up. Efficacy measures with the IRLS score were superior to placebo with the 2 mg/day and 3 mg/day doses. The retention rate over 6 months was 63%, with adverse events being the most common cause of discontinuation (20%).

Efficacy and safety were evaluated in a 6-week, randomized, placebo-controlled, dose-finding trial comparing five different doses (0.5 mg/24 hours, 1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours, 4 mg/24 hours) in 341 patients.⁴² The lowest dose was ineffective, but all others proved to be superior to placebo, with a dose-dependent response observed except for the 4 mg/24 hour dose, in which no additional benefit was detected compared to the 3 mg/24 hour dose.

Table 3 Randomized controlled trials of rotigotine in RLS

Clinical trial	Methodology	Results of efficacy (IRLS sum score versus baseline)	Side effects reported in >5% patients
Stiasny-Kolster et al ³⁸	1-week pilot trial 63 patients randomized to placebo or rotigotine, 1.125 mg, 2.5 mg, or 4.5 mg	Placebo: -7.7 1.125 mg: -10.5 2.5 mg: -12.3 4.5 mg: -15.7*	Application site reaction, 26.5% Headache, 22.4%
Oertel et al ⁴²	6 weeks 341 patients randomized to placebo or rotigotine, 0.5 mg/24 hours, 1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours, or 4 mg/24 hours	Placebo: -9.3 0.5 mg/24 hours: -10.5 1 mg/24 hours: -15.1* 2 mg/24 hours: -15.7* 3 mg/24 hours: -17.5* 4 mg/24 hours: -14.8*	Application site reaction, 17.5% Nausea, 14.4% Headache, 7.7% Fatigue, 6.7%
Trendwalker et al ⁴⁰	6 months 458 patients randomized to placebo or rotigotine 1 mg/24 hours, 2 mg/24 hours, or 3 mg/24 hours	Placebo: -8.6 1 mg/24 hours: -13.7* 2 mg/24 hours: -16.2* 3 mg/24 hours: -16.8*	Application site reaction, 43% Nausea, 16% Headache, 13% Fatigue, 13%
Oertel et al ³⁹	4 weeks 67 patients randomized to placebo or rotigotine (1:2) with titration up to optimal dose (1 mg/24 hours to 3 mg/24 hours) Polysomnographic assessment of periodic limb movement	Placebo: -9.9 Rotigotine: -16.9*	Application site reaction, 17.4% Nausea, 21.7% Headache, 17.4% Fatigue, 8.7% Somnolence, 10.9% Constipation, 6.5% Insomnia, 6.5% Dizziness, 6.5%
Hening et al ⁴¹	6 months 505 patients randomized to placebo or rotigotine 0.5 mg/24 hours, 1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours	Placebo: -9.0 0.5 mg/24 hours: -10.9 1 mg/24 hours: -11.1 2 mg/24 hours: -13.4* 3 mg/24 hours: -14.3*	Application site reaction, 27% Nausea, 18.1% Headache, 11.6% Fatigue, 7% Somnolence, 11% Pruritus, 5% Dizziness, 5%

Note: *Indicates statistical significance compared to placebo ($P < 0.05$).

Abbreviations: RLS, restless legs syndrome; IRLS, International Restless Legs Severity scale.

Over the 1-year open extension of this study,⁴³ the retention rate was 74.6%. Discontinuation was most commonly explained by adverse events (17%), most of which were application site reactions. Efficacy was maintained with a 17.4 decrease in the IRLS score. Tolerability was considered to be “good” or “very good” in a large proportion of the remaining patients (80.3%). The most common adverse event was local skin reaction, which led to discontinuation of the drug in 13.2% of patients. Nausea and fatigue were the two other side effects most frequently reported. Augmentation was not evaluated in a standardized way, and no patients reported occurrence of these symptoms. A 5-year open extension study of the same cohort revealed that efficacy remained substantial over the years.⁴⁴ However, the retention rate was somewhat low (43% of patients entering the open label extension phase). Adverse events were the most common reason for discontinuation (30% of the cohort). Application site reaction was frequent (58%), and led to discontinuation in 19% of patients. Lack of efficacy led to treatment interruption in 11% of patients. Clinically significant augmentation was retrospectively assessed, and was reported in 13% of patients. In the patients who completed the study, 39% were free of RLS symptoms, and the mean IRLS score had declined from 27.9 to 9.0 (maximal score of 40). This trial suggested that rotigotine was suitable for long-term treatment in patients with moderate to severe RLS. A post hoc analysis including patients taking approved dosages (1 mg/day, 2 mg/day, or 3 mg/day) indicated that only 23% of them completed the 5 years of follow-up.⁴⁵ Forty percent were excluded because of adjustment of medication outside of this range, and 37% stopped while taking appropriate dosage, mostly because of adverse events (25%) or less frequently because of lack of efficacy (6%). Efficacy outcomes were maintained through the 5 years of follow-up in the remaining patients.

Altogether, these studies provided strong data supporting the efficacy of rotigotine over placebo, both in the short- and long-term treatment of RLS. Regarding the high drop-out rate in the open-label phase extension studies, tolerability seems to remain a significant limiting factor, and will be further discussed here.

Adverse and side effect profile of rotigotine

Dopaminergic receptor stimulation is accompanied by side effects that are common to all drug formulations, including nausea, drowsiness, sleep attacks, and compulsive behavior, all of which need to be closely monitored. Rotigotine is also specifically associated with local skin reactions arising in

approximately half of patients, and they are mostly mild in intensity, but they are still a frequent cause of discontinuation in clinical trials.

Impulsive behavior caused by dopaminergic therapy is a serious complication that can have disastrous consequences for patients. Hypersexuality, compulsive overeating, pathological gambling, and punting have been reported in some patients treated with rotigotine for Parkinson's disease.^{46,47} In these case reports, patients received between 6 mg and 22.5 mg per day of rotigotine, and all of the patients were also taking levodopa. None of the placebo-controlled trials that led to the approval of rotigotine in the treatment of RLS reported significant increases in this complication. However, a recent retrospective study of a small cohort of 28 patients reported rates of impulsive behavior as high as 21%.⁴⁸ These patients had no prior history of such behavior, and this complication occurred even in individuals taking low doses of rotigotine (mean 3.8 mg/day). This data is useful in reminding clinicians to be aware of this problem, even with low doses of dopaminergic agonists, in order to detect it.

Sleep attacks while driving were not reported in clinical trials assessing rotigotine in RLS; however, they occurred in one patient taking the 13.5 mg dose in the treatment group of a trial for Parkinson's disease.³³ One patient also lost consciousness while driving in this trial; he was receiving a dose of 18 mg. A case report also described sleep attacks in a patient with Parkinson's disease on 8 mg/24 hours of rotigotine.⁴⁹ To our knowledge, these effects have not yet been described in RLS, and this may be attributable to the lower dosage used for this disorder.

It was expected that the continuous delivery system of the transdermal therapy could lower or even abolish augmentation rates, based on the hypothesis that development of augmentation is related to the pulsatile stimulation of dopaminergic receptors. However, augmentation was reported in a significant proportion of patients (18% to 43%) during clinical trials, although it was rarely severe enough to lead to discontinuation of therapy.^{39–42} As mentioned earlier, long-term treatment was well tolerated, with only 13% of patients developing augmentation over 5 years of therapy.⁴⁴ It should be reminded, however, that patients with significant side effects, including augmentation, were not included in the extension phase study, which may explain the lower risk observed compared to the placebo-controlled trial. A recent retrospective study showed that none of the 748 patients treated for 18 months with rotigotine discontinued the treatment because of augmentation. The authors concluded that clinically relevant augmentation was rare with rotigotine, and

was probably lower compared to other dopamine receptor agonists.⁵⁰ The study with Japanese subjects reported a similar, very low risk of augmentation (2.7%) in the extension phase study.⁵¹ The retrospective nature of these studies and the lack of control medication in the extension phase may effectively introduce bias in the final interpretation of the harvested data. However, the relative absence of augmentation in these patients is encouraging and implies that continuous delivery of the drug helps to prevent this complication more effectively than with the pulsatile dopaminergic stimulation seen with orally taken agents. Head-to-head comparisons of rotigotine with other dopamine receptor agonists in a prospective fashion would be the best way to put this issue to rest.

Nausea with rotigotine has been consistently reported in trials, affecting 16% to 22% of patients receiving the drug.^{39–42} Dizziness and somnolence were also reported,^{26,39,41} with somnolence being dose-dependent in one study.⁴¹ In the aforementioned placebo-controlled trials, nondopaminergic-related adverse events with a $\geq 5\%$ incidence included headache and augmentation.^{39–42} Cardiac safety was evaluated with supratherapeutic doses of rotigotine (24 mg/24 hours) in patients with advanced Parkinson's disease, with no significant consequence on QT/QTc intervals.⁵² In RLS trials, prolongment of the QT interval has been reported in one patient receiving 4 mg/day.⁴³

Therapeutic options: alternatives

Avoiding exacerbating factors should always be considered part of the treatment plan. Dopamine receptor antagonists like antinausea drugs, neuroleptics, or some antidepressants may cause or worsen symptoms of RLS. Iron therapy is controversial, but considering its safety profile, it seems acceptable to treat patients with a low ferritin level.⁵³ Some anticonvulsant drugs may be used to treat RLS. Gabapentin, and its prodrug, gabapentin enacarbil (FDA approved in 2011), are effective and well tolerated.⁵⁴ Some data also support the use of pregabalin. Evidence for efficacy with other anticonvulsants, including carbamazepine, is weaker.^{23,26} Opioids should not be considered as first-line agents, but they represent an excellent option for patients not getting sufficient relief from other drug categories. With careful monitoring of doses, tolerance and dependence can be avoided. Sufficient data supports the usage of oxycodone, while the use of methadone and tramadol are considered investigational.²⁶

Guidelines for RLS therapy

The American Academy of Sleep Medicine has recently published a clinical practice guideline on the treatment of RLS.²⁹

The levels of recommendation were graded as “standard,” “guideline,” or “option,” based on the level of evidence and on the benefit-to-harm ratio. Therapies with a “standard” level of recommendation included pramipexole and ropinirole. A “guideline” level of recommendation was given to levodopa with dopa decarboxylase inhibitor, opioids, gabapentin enacarbil, and cabergoline. Therapies with an “option” level of recommendation include carbamazepine, gabapentin, pregabalin, clonidine, and iron supplementation in patients with low ferritin levels. Pergolide received a “standard against” level of recommendation because of the risks of heart valve damage with this medication. No recommendations were made initially on rotigotine despite high levels of evidence for its efficacy. Following its approval by the FDA in April 2012, an update of these guidelines was published, and rotigotine has received a “guideline” level of recommendation, on par with the other dopaminergic therapies.⁵⁵

European guidelines provided level A recommendations for the short-term control of symptoms with rotigotine, pramipexole, ropinirole, gabapentin, gabapentin enacarbil, and pregabalin.²⁸ For the purpose of long-term therapy, rotigotine was considered effective, gabapentin enacarbil was probably effective, and ropinirole, pramipexole and gabapentin were considered possibly effective.

Conclusion

In conclusion, RLS is a frequent, although under-diagnosed condition that may cause significant morbidity in some individuals. Etiology is unknown, although robust evidence suggests that genetic factors play an important role in its genesis. Many treatment options are available. Dopamine receptor agonists are considered the first-line therapy when daily treatment is needed. Rotigotine is the only FDA-approved transdermal drug for this disorder. This continuous delivery system may help control daily RLS symptoms, and has been shown to be superior to placebo in multiple trials. Long-term usage has been shown to provide sustained efficacy for at least 5 years. Adverse effects related to dopaminergic stimulation, like nausea, impulsive behavior, and augmentation, may occur and call for physician awareness and regular follow-up appointments to detect their occurrence and to determine an appropriate intervention plan.

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Disclosure

The authors report no conflicts of interest in this work.

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