Treating restless legs syndrome with rotigotine

Restless legs syndrome has attracted increasing interest as a clinically significant, common and treatable disorder. Good evidence suggests that dopaminergic drugs are the most effective first-line agents when symptoms are severe.

This article explores the clinical recognition of restless legs syndrome and the rationale for offering dopaminergic therapy. It also looks at the latest drug to gain approval for treating restless legs syndrome, the novel transdermal dopamine agonist patch, rotigotine (Neupro, UCB Pharma Ltd, Slough).

Diagnosing restless legs syndrome

Restless legs syndrome is undoubtedly an under-recognized phenomenon given that epidemiological studies suggest a prevalence of at least 10% in Caucasian populations (Allen et al, 2005). Although it is experienced as an infrequent and inconsequential symptom in the majority of cases, there is a clear spectrum of severity. Patients with severe cases report symptoms that dramatically affect their quality of life, especially with regard to the sleep–wake cycle. Such patients often benefit greatly from timely recognition of restless legs syndrome and its subsequent treatment.

Restless legs syndrome is probably a symptom complex that reflects the final common pathway to a variety of processes. Although they are often identical in nature, it is common to divide restless legs syndrome into 'primary' and 'secondary' forms. The latter include predisposing factors such as iron deficiency, pregnancy, renal failure and peripheral neuropathies. The former often has a familial basis, especially if symptom onset occurs before the age of 45 years.

In principle, once it has been considered as a possibility, diagnosing restless legs syndrome is straightforward, provided a reliable history is available. Four key diagnostic criteria have been established by the International Restless Legs Syndrome Study Group (IRLSSG) (Allen et al, 2003):

1. An urge to move the legs or, less frequently, other body parts, usually with an associated unpleasant sensory phenomenon in the affected limb(s)
2. Onset or significantly worse symptoms in the evening or at night
3. Onset or worsening symptoms when sitting or lying down at rest
4. Symptoms are temporarily improved by activity or movement.

Supporting evidence for a positive diagnosis includes a family history of similar symptoms, the presence of regular limb jerks when asleep or drowsy, so-called periodic limb movements and a clear response to dopaminergic medication.

Apart from the associated sensory discomfort, restless legs syndrome can seriously disrupt the quality and quantity of nocturnal sleep with significant implications for impaired daytime performance. Increasing evidence also suggests an association with hypertension, mood and even cognitive disturbance.

Current theories of pathophysiology

Despite numerous associations and interesting genetic evidence, a unifying theory regarding the underlying causes and pathophysiology of restless legs syndrome is lacking. From its earliest description, a link with low iron stores has been clear and iron replacement, perhaps intravenously, has been used as an effective symptomatic treatment in the absence of good controlled data (Norlander 1953; Earley et al, 2009). Even if iron stores seem adequate, brain levels of iron, particularly in subcortical motor areas such as the substantia nigra and red nucleus, appear reduced in restless legs syndrome patients (Allen and Earley, 2007). Why reduced brain iron availability should cause restless legs syndrome remains unclear. Many have pointed out that iron is an essential co-factor in the rate-limiting enzyme for dopamine synthesis, tyrosine hydroxylase, such that low levels may lead to a 'functional' dopamine deficiency. The fact that levels of iron fluctuate through the day with low values at night in the periphery and brain has also been proposed to explain the circadian influence on restless legs syndrome symptomatology (Unger et al, 2009).

The possible involvement of dopamine in restless legs syndrome was first considered after the serendipitous discovery in 1982 that dopamine replacement therapy for Parkinson's disease also improved co-existent symptoms of restless legs syndrome (Akpinar, 1982). To date, objective evidence that there is a definite disturbance of dopaminergic pathways in restless legs syndrome remains scanty. However, attention has focussed on the hitherto

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poorly characterized dopaminergic pathway from the hypothalamus to the spinal cord, the A11 neuronal group (Clemens et al, 2006). This small nucleus comprises only around 300 neurons in the rat but may have an important neuro-modulatory role via its widespread projections to sensory afferents in the dorsal horn of the spinal cord or possibly the sympathetic nuclei in the infero-mediolateral portions. Assuming dopamine has an inhibitory role, reduced activity in this pathway might disinhibit normal incoming sensory phenomena to cause restless legs syndrome symptoms. Similar effects involving motor loops might account for periodic limb movements, especially since these movements usually resemble a slow spinal flexor withdrawal reflex. Limited evidence from animal models suggests that small specific lesions of the A11 region may cause phenomena interpretable as restless legs syndrome in rats, especially if they are iron deficient.

The notion that the spinal cord is somehow 'irritable' in restless legs syndrome may have relevance for the evolving story regarding identified susceptibility genes for restless legs syndrome. From large genome-wide studies in various populations, at least four genes confer significant risk for developing restless legs syndrome (Mignot, 2007; Schormair et al, 2008). Contrary to expectations, the products of these genes do not appear to be directly associated with either iron or dopamine metabolism. Although yet to be fully characterized, at least some of the gene products are likely to be more involved in embryonic development, guiding motor and sensory axonal connectivity. This may explain the putative 'faulty wiring' in the spinal cord of restless legs syndrome patients.

Many unexplained key phenomena remain such as the diurnal pattern of symptoms, the inherent periodicity of periodic limb movements and why movements per se should relieve sensory discomfort.

Treating restless legs syndrome

Once restless legs syndrome has been recognized as a significant clinical problem, potentially reversible causes should be addressed. In particular, the serum level of ferritin should be checked, even in the absence of frank anaemia. Levels less than 45 μg/litre suggest low iron stores and subsequent iron replacement therapy may improve restless legs syndrome symptoms. Other factors may also worsen underlying restless legs syndrome and should be addressed. For example, most antidepressants will exacerbate symptoms and should be discontinued if at all possible. Dopaminergic antagonists including many antiemetics may also worsen or even provoke restless legs syndrome.

Judging whether symptomatic drug treatment is appropriate for individual restless legs syndrome patients is a clearly a clinical decision. However, if symptoms are moderately severe, occurring more than several days each week, or if the adverse consequences on the sleep–wake cycle are significant, it is usual practice to offer drug therapy. The available evidence suggests that dopaminergic therapy is the most effective approach. Initially l-dopa was used but the newer generation of dopamine agonists are now generally considered first line at doses far less than those used for Parkinson's disease. Non-ergot agonists such as pramipexole and ropinirole are preferred because of potential long-term side effects of dangerous fibrotic reactions with the ergot class. If sensory symptoms predominate, neuropathic pain agents such as gabapentin, pregabalin and carbamazepine may be used successfully, occasionally together with dopaminergic drugs. A second-line approach is to use opiates such as dihydrocodeine or tramadol. In addition, when sleep disruption is particularly severe, relatively non-specific hypnotic agents such as clonazepam may improve symptom control.

Rotigotine is a dopamine agonist delivered by the transdermal route that has been used in early and late-stage Parkinson's disease for several years (Baldwin and Keating, 2007). Increasing evidence from controlled trials and long-term follow-up studies suggests that it may also be particularly suitable for the treatment of moderate and severe restless legs syndrome (Stiasny-Kolster et al, 2004; Oertel et al, 2008a, c; Trenkwalder et al, 2008).

The potential benefits of rotigotine

Rotigotine is a silicone-based non-ergot dopamine agonist with particular affinity for the D_2 receptor (Bunten and Happe, 2006). Activity is also seen at D_1 and D_3 as well as 5-HT_{1a} receptors, while it is an antagonist to α_2 adrenergic receptors. It has low oral bioavailability because there is an extensive first-pass effect and is therefore delivered as a transdermal patch. This mode of delivery appears to allow steady and continuous dopaminergic stimulation within 2–3 days, assuming once daily application. Although direct evidence is lacking, it has been proposed that this feature may improve tolerability.

Although dopaminergic drugs in general are usually clinically effective in restless legs syndrome, the fairly common phenomenon of augmentation with regular use can cause problems with symptom control, especially with the shorter-acting drugs such as l-dopa (Allen and Earley, 1996). Augmentation refers to the development of restless legs syndrome symptoms earlier in the day than previously experienced, often with increased intensity and the involvement of other body parts such as the arms. This can be viewed as a form of rebound, occurring when drugs are initially taken mid- or late evening. Augmentation is usually managed either by splitting the dose of dopaminergic drug or switching to an alternative agent, ideally one that is long acting.

Several randomized placebo-controlled trials and subsequent open label follow-up studies have now assessed

the efficacy and tolerability of rotigotine in primary restless legs syndrome (*Table 1*). The first major trial (Stiasny-Kolster et al, 2004) was primarily a dose-finding study which lasted 6 weeks and recruited 333 patients with moderately severe restless legs syndrome as gauged by the IRLS (IRLSSG Severity Rating Scale) (Walters et al, 2003). These patients had longstanding restless legs syndrome and 88% had previously been taking other dopaminergic drugs. A 7-day washout occurred before patch treatment was started. Mean IRLS scores were 28 out of a possible maximum of 38. Doses of 1–4 mg daily significantly reduced the IRLS score by around 15 in the 310 who completed the trial with no clear dose effect over this range. As with other restless legs syndrome trials, a relatively large placebo response was noted with a 9-point drop in the scale and a responder rate of 42%. Secondary end-points including quality of life measures also improved in the treated subgroups. Minor adverse events were seen in 62% of actively treated patients compared to 46% for the placebo group. Local minor application site reactions were the commonest side effect but overall tolerability seemed very good.

A second European trial (SP790) was conducted over 6 months in 447 subjects with severe primary restless legs syndrome (Trenkwalder et al, 2008). Remarkably similar results to the previous study were obtained in terms of reductions in the IRLS score, degree of placebo response and improved secondary end-points. All three doses (1, 2, and 3 mg) produced significant dose-dependent results compared to placebo at 6 months.

A similar 6-month trial was completed in the USA (SP792) (Hening et al, 2008). Broadly similar results were obtained in a slightly less affected group of restless legs syndrome patients (mean IRLS score around 23).

All these trials rely on subjective data, potentially explaining the high placebo response. However, in a laboratory-based trial assessing associated periodic limb movement data, very significant reductions in the periodic limb movement index were seen on treatment (doses 1–3 mg). In particular, the number of periodic limb movements per hour during sleep fell from 51 to 8 in the treated group, yet only from 37 to 27 in the placebo arm (Oertel et al, 2008b). In this study 26% of patients were rendered completely symptom free on treatment with no equivalent response on placebo.

Regarding long-term follow up, published data from 1 year are available (Oertel et al, 2008c). In brief, response rates are maintained with reductions in baseline IRLS scores by 17. These responses are mirrored by corresponding improvements in quality of life data. When studied, there have been no reports of augmentation in the long-term datasets (Oertel et al, 2008c; Trenkwalder et al, 2008).

Tolerability data suggest few major problems with rotigotine. Although the majority of studies have a high level of application-site reactions, these are rarely severe or enough to produce discontinuation and most often reflect slight erythema.

In some Parkinson's disease patients, use of dopamine agonists in particular has been strongly associated with the development of inappropriate or impulsive behaviours such as compulsive gambling or hypersexuality (Weintraub, 2008). In general, doses used in restless legs syndrome treatment are much lower and this phenomenon is probably very rare. However, a few case reports have emerged in the context of restless legs syndrome treatment with dopamine agonists and patients should perhaps be forewarned of this possible side effect (Tippmann-Peikert et al, 2007). At the time of writing, no such cases have yet been reported with rotigotine.

Table 1. Overview of four trials assessing rotigotine in idiopathic restless legs syndrome

	Reference and study type			
	Stiasny-Kolster et al (2004) Double-blind placebo controlled	Oertel et al (2008a) Double-blind placebo controlled	Oertel et al (2008c) Open label, single arm	Trenkwalder et al (2008) Double-blind placebo controlled
Study duration	1 week	6 weeks	1 year	6 months
Number of patients	63	333	295	447
Mean age	58	58	58	58
Female %	64	68	66	71
Mean IRLS severity (range where available)	26 (16–38)	28	28	28 (15–40)
Dose range	0.5–2 mg	0.5–4 mg	mean 2.8 mg	1–3 mg
Mean reduction in IRLS score (at most effective dose)	16 (2 mg)	18 (3 mg)	17	17 (3 mg)
Mean reduction in IRLS score on placebo	8	9	–	9

IRLS = International Restless Legs Syndrome Study Group Severity Rating Scale. *The homogeneity of the patients' groups and their response to treatment and placebo is striking.

Conclusions

For a variety of reasons, restless legs syndrome has faced a struggle to gain acceptance as a credible phenomenon worthy of formal diagnosis and treatment. The name of the syndrome itself, to some, does not imply a 'serious' condition and the fact that it is so prevalent, usually as a minor problem, potentially 'devalues' its clinical importance. The fact that restless legs syndrome may present to a variety of medical specialities has also led to problems establishing a 'home' for the condition in any one discipline. However, increasing neurobiological evidence, particularly from genetic studies, has fuelled considerable interest in both the nature of restless legs syndrome and its treatment. In addition, accumulating data on the potential consequences that severe restless legs syndrome has on quality of life issues and the sleep–wake cycle, as well as general health measures such as blood pressure, have helped to elevate its status.

It remains an enigma why dopamine replacement should be quite so effective as a symptomatic therapy in restless legs syndrome. In the absence of hard evidence, the notion that the spinal cord is effectively depleted of dopamine in restless legs syndrome has heuristic appeal, although, if this were the main explanation, one might expect all dopamine deficiency states to display restless legs syndrome symptomatology. This is not the case as, overall, it does not appear to be appreciably more common in Parkinson's disease, for example.

The rotigotine patch is a novel, effective and well-tolerated approach to treating moderately severe restless legs syndrome. Whether it is more efficacious with fewer side effects than pre-existing oral (dopaminergic) therapies is open to debate given the lack of head to head trial data. However, there are theoretical reasons and some long-term follow-up data to suggest that troublesome phenomena such as augmentation may be less apparent with a long-acting agent such as rotigotine. It is likely that patient choice and personal experience with the agent will be important factors in selecting or recommending this particular therapy for restless legs syndrome. **BJHM**

Conflict of interest: Dr Reading has participated in a UK advisory group for rotigotine use in restless legs syndrome and has received honoraria for involvement in educational meetings sponsored by UCB Pharma Ltd.

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KEY POINTS

- Owing to its high prevalence and spectrum of severity, restless legs syndrome is often overlooked as an easily recognized, potentially disabling yet treatable long-term condition.
- Dopaminergic therapy is now regarded as the first-line treatment for moderate or severe restless legs syndrome.
- The latest dopamine agonist therapy to gain a licence for restless legs syndrome is the novel transdermal dopamine patch, rotigotine.
- Once-daily effective doses of rotigotine in restless legs syndrome are considerably lower than those routinely used in Parkinson's disease.