

Potential of the Rotigotine Transdermal Patch for Patients with Advanced Parkinson's Disease

The symptomatic burden of Parkinson's disease (PD) can be managed effectively for long periods, although no disease-modifying treatments have been developed. The clinical diagnosis of PD is based on the presence of cardinal motor features, which include tremor at rest, rigidity, bradykinesia and postural instability.¹ The initial motor symptoms of PD have been attributed primarily to dopamine deficiency arising from degeneration of the substantia nigra.²

Early motor symptoms of PD can be controlled by dopamine agonists or levodopa. Dopamine agonists are often used as a first-line option because they delay the onset of motor fluctuations and dyskinesia associated with prolonged levodopa use;¹ however, the attenuation of disease-related symptoms tends to be less pronounced with dopamine agonists than with levodopa. As PD progresses, symptom control with dopamine agonist monotherapy inevitably diminishes to a point where treatment with levodopa becomes a necessity.¹

Parkinson's disease: a progressive condition

It is now recognised that, in addition to degeneration of the nigrostriatal dopaminergic pathway, a variety of neuronal systems are involved in PD.² PD is associated with progressive loss of monoaminergic and cholinergic neurons, initially at the level of the brainstem, but later involving subcortical and cortical regions. Dysfunction of non-dopaminergic cells is thought to play a role in development of non-motor symptoms,³ including autonomic dysfunction, cognitive and psychiatric changes, sensory symptoms and sleep disturbances.^{4,5} Although these non-motor symptoms can occur at an early stage, they tend to dominate the clinical picture in advanced PD and are a major contributor to disability and impaired quality of life.⁴

Advanced PD is also characterised by development of motor complications associated with long-term

dopaminergic therapy. These motor complications typically begin with minor motor fluctuations, often after four to five years of therapy, and progress to significant dyskinesia and akinetic periods after 10–15 years.^{6,7} Pulsatile stimulation of dopamine receptors is thought to play a significant role in this process,⁸ leading to the hypothesis that continuous dopaminergic stimulation (CDS), such as through treatment with the rotigotine transdermal patch, may ameliorate or prevent development of motor complications.⁹

The rotigotine transdermal patch

Rotigotine is a non-ergolinic dopamine agonist with a receptor profile similar to that of dopamine¹⁰ and is formulated in a once-daily transdermal patch that provides continuous, uniform release over 24 hours.¹¹ The clinical studies of the rotigotine transdermal patch in early PD,^{12,13} which reported efficacy with good tolerability, were reviewed previously in *Advances in Clinical Neuroscience and Rehabilitation*.¹⁴ These results provided the basis for approval of the transdermal rotigotine patch for use in early PD. More recently, the rotigotine transdermal patch was approved for the treatment of idiopathic PD, either with or without concomitant levodopa therapy. When used in combination with levodopa, the transdermal patch can be used to deliver rotigotine doses of up to 16mg/24 hours.

Clinical studies of rotigotine in advanced PD

The efficacy and tolerability of the rotigotine transdermal patch were compared with placebo in a phase III trial in 351 patients with advanced PD.^{15,16} Patients were randomised to receive transdermal rotigotine 8 or 12mg/24 hours, or placebo, with titration to the randomised dose over a four-week period followed by a four-week maintenance phase. Both doses of transdermal rotigotine resulted in statistically significant decreases from baseline in absolute 'off' time compared with placebo (Figure 1). These decreases in 'off' time were associated with an increase in 'on without troublesome dyskinesia' time (Figure 2). Though there was a greater reduction in 'off' time for the 8mg/day rotigotine group compared to the 12mg/day group, this difference was not significant in a post hoc analysis. In fact, the apparent increase in treatment effect with 8mg/day became evident during the titration phase when daily rotigotine intake was the same for each group (Figure 2).¹⁶

Further evidence of the efficacy of the transdermal rotigotine patch was provided by a phase III placebo- and pramipexole-controlled trial in which 604 patients with advanced PD were randomised to rotigotine, pramipexole or placebo in a ratio of 2:2:1.¹⁷ Rotigotine doses were titrated weekly in 2mg/24 hours increments to an optimal response or a maximum dose of 16mg/24 hours. Patients receiving pramipexole were titrated weekly to an optimal response or a maximum dose of 4.5mg/day (expressed as the salt formulation of pramipexole; base equivalent 3.3mg/day). Patients



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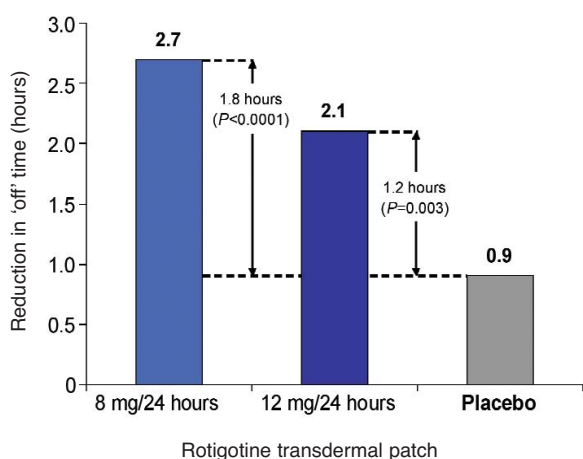


Figure 1: Reduction in 'off' time between baseline and the end of the maintenance phase in a phase III placebo-controlled trial in patients with advanced Parkinson's disease.

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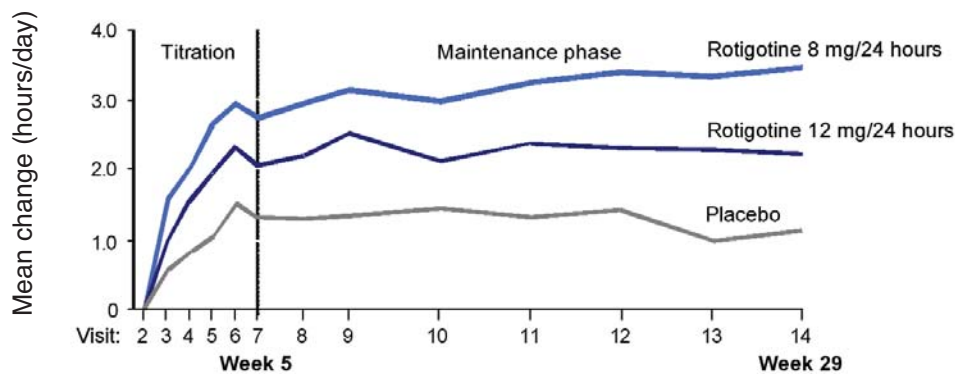


Figure 2: Increase in 'on without troublesome dyskinesia' time between baseline and the end of the maintenance phase in a phase III placebo-controlled trial in patients with advanced Parkinson's disease.

receiving the rotigotine transdermal patch or pramipexole had a significant decrease in 'off' time from baseline (Figure 3) and an increase in time spent 'on without troublesome dyskinesia' (rotigotine +2.8 hours/day, pramipexole +2.7 hours/day and placebo +1.4 hours/day). The transdermal rotigotine patch was non-inferior to pramipexole for reduction in 'off' time and, in addition, was associated with an increase in time spent 'on without troublesome dyskinesia'. The results from both phase III trials of the transdermal rotigotine patch in advanced PD provide a helpful indication of the type and rate of adverse events which occur with this treatment. In the phase III placebo-controlled trial, the most frequent adverse events were application-site reactions (rotigotine 41% vs placebo 13%), somnolence (31% vs 27%), nausea (24% vs 18%), dizziness (19% vs 15%), dyskinesia (15% vs 7%) and oedema (11% vs 1%).¹⁵ These events are typical of those in patients with PD or who are treated with other dopaminergic drugs or alternative transdermal systems.¹⁵ In the placebo- and pramipexole-controlled trial, adverse events occurred with similar frequency in each of the active treatment groups, with the exception of psychiatric adverse events, which were more frequent with pramipexole (21.3%) than rotigotine (14.6%) or placebo (11.1%), and application-site reactions, which were more frequent with rotigotine (20.5%) than pramipexole (8.4%) or placebo (10.1%).¹⁷

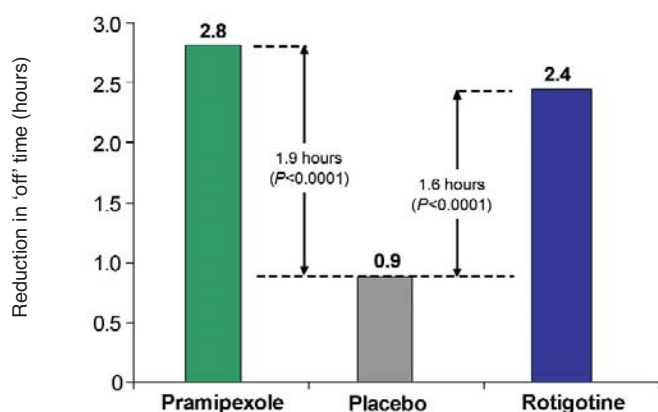


Figure 3: Reduction in 'off' time between baseline and the end of the maintenance phase in a phase III placebo- and pramipexole-controlled trial in patients with advanced Parkinson's disease.

The potential of the rotigotine transdermal patch in advanced PD

A recent change to the marketing authorization now allows rotigotine to be used in combination with levodopa at doses up to 16mg/24 hours, which means that patients who progress from early to advanced PD can continue to receive treatment in combination with levodopa, even if they require high dopamine agonist doses.

The rotigotine transdermal patch has been shown to provide effective control of some non-motor symptoms in patients with advanced PD. These non-motor symptoms include sleep disturbances, which may arise as a consequence of degeneration of central sleep

regulation centres in the brainstem and thalamocortical pathways.⁴ Long-acting dopamine agonists (such as the rotigotine transdermal patch and the ergot-derived dopamine agonist cabergoline) may provide relief for patients with sleep disturbances.^{18,19,20} Furthermore, as noted above, the phase III placebo- and pramipexole-controlled study showed that treatment with the rotigotine transdermal patch was associated with a decreased probability of waking up in an 'off' state and an increased likelihood of waking up 'on without dyskinesia'.¹⁷ A single-arm study in PD patients with unsatisfactory control of early-morning motor impairment showed that the rotigotine transdermal patch had positive effects on motor and non-motor variables, including nocturnal akinesia, dystonia and cramps score, Epworth Sleepiness Scale, and number of nocturias.²¹ In addition to improving motor and non-motor symptoms, transdermal rotigotine might reduce the number of pills that the patient with dysphagia has to take.

Data from experimental models shows that continuous rotigotine delivery provides CDS. In freely moving non-parkinsonian rats, subcutaneous injection of an oily crystalline rotigotine suspension, which mimics the kinetics of transdermal administration, increased locomotor activity throughout a 48-hour period and led to stable extracellular dopamine levels.²² These findings were supported by a study in marmosets, which showed that continuous rotigotine administration resulted in good locomotor activity and improved motor disability throughout the day.²³

The potential for CDS to reverse levodopa-induced motor complications has been demonstrated in studies of continuous infusions of apomorphine,^{24,25,26,27,28} intrajugal carbidopa/levodopa²⁹ and lisuride.³⁰ However, continuous infusions are expensive and impractical for large numbers of patients.⁹ Therefore, the rotigotine transdermal patch may provide a convenient means of delivering CDS without the need for continuous infusion. In addition to improving motor complications, CDS may also have the potential to alleviate sleep disturbances, prevent the development of gastrointestinal dysfunction and reduce the risk of developing psychosis or behavioural disturbances.⁹ These possible benefits require investigation in large, well-designed clinical trials.

Summary

Delivery of CDS with the rotigotine transdermal patch may have the potential to alleviate motor complications and has been shown to significantly reduce 'off' time in clinical trials in advanced PD. Advanced PD is characterised by motor complications associated with long-term dopaminergic therapy. The available evidence suggests that the rotigotine transdermal patch is a valuable addition to the therapeutic options for patients with advanced PD.

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Neupro® Rotigotine

Prescribing Information

Presentation: Neupro® is a thin, matrix-type square transdermal patch.

Neupro 2 mg/24 h transdermal patch: Releases 2 mg rotigotine over 24 hours. 10cm² patch contains 4.5 mg rotigotine.

Neupro 4 mg/24 h transdermal patch: Releases 4 mg rotigotine over 24 hours. 20cm² patch contains 9.0 mg rotigotine.

Neupro 6 mg/24 h transdermal patch: Releases 6 mg rotigotine over 24 hours. 30cm² patch contains 13.5 mg rotigotine.

Neupro 8 mg/24 h transdermal patch: Releases 8 mg rotigotine over 24 hours. 40cm² patch contains 18.0 mg rotigotine.

Indications: To treat the signs and symptoms of idiopathic Parkinson's disease, either with or without concomitant levodopa therapy.

Dosage: Neupro is applied to the skin once a day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different application site. In monotherapy, treatment is initiated with a single daily dose of 2 mg/24 h. Dose increased by 2 mg/24 h each week (e.g. 2 mg/24h in Week 1, 4 mg/24 h in Week 2, 6 mg/24 h in Week 3 and 8 mg/24 h in Week 4), until an effective dose is reached. Maximal dose is 8 mg/24 h. In combination with levodopa, treatment initiation is at 4 mg/24 h and increased weekly in 2 mg increments, up to a maximum dose of 16 mg.

Contraindications: Hypersensitivity to rotigotine or to any

of the excipients. Neupro should be removed prior to Magnetic Resonance Imaging (MRI) or cardioversion to avoid burns.

Warnings and Precautions: External heat should not be applied to the patch. Dopamine agonists are known to cause hypotension, and monitoring of blood pressure is recommended. Where somnolence or sudden sleep onset occurs, or where there is persistent, spreading or serious skin rash at the application site, consider dose reduction or termination of therapy. Rotate the site of patch application to minimise the risk of skin reactions. In case of generalised skin reaction associated with use of Neupro, discontinue treatment. Avoid exposure to direct sunlight until the skin is healed. If treatment is to be withdrawn, it should be gradually reduced to avoid symptoms of neuroleptic malignant syndrome.

Compulsive behaviours and hallucinations have been reported in patients treated with Neupro. Do not administer neuroleptics or dopamine antagonists to patients taking dopamine agonists. Caution is advised when treating patients with severe hepatic impairment, and in patients taking sedating medicines or other depressants in combination with rotigotine. Switching to another dopamine agonist may be beneficial for those patients who are insufficiently controlled by rotigotine.

Undesirable effects: Very common side effects include nausea, vomiting, somnolence, dizziness and application site reactions. Common side effects include anorexia, hallucinations, sleep attacks, insomnia, abnormal dreams, headache, dyskinesia, lethargy, orthostatic hypotension, hypertension, hiccup, cough, constipation, diarrhoea, dry

mouth, dyspepsia, hyperhidrosis, erythema, pruritus, asthenic conditions and peripheral oedema. Uncommonly, syncope, loss of consciousness, visual disturbances, or hypotension may occur. Rarely, psychotic disorders, increased libido or convulsion may occur.

Basic NHS Cost: Starter Pack: £110.34

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