

# The Rotigotine Transdermal Patch May Provide Continuous Dopaminergic Stimulation in Early-Stage Parkinson's Disease

Parkinson's disease is a common disorder. Estimates of the prevalence of Parkinson's disease in Europe vary from 65–1250 per 100,000 people, with the variations possibly due to environmental or genetic factors or as a consequence of methodological differences or variation in age distribution between studies.<sup>1</sup> Similarly, estimates of the incidence of Parkinson's disease range from five to 346 cases per 100,000 people per year.<sup>1</sup>

Parkinson's disease is characterised by motor symptoms, particularly bradykinesia and rigidity, which are attributed primarily to dopamine depletion after loss of neurons from the nigrostriatal pathway.<sup>2</sup> However, progressive loss of other neuronal pathways, including serotonergic, noradrenergic and cholinergic systems, also contributes to the pathology of this disorder.<sup>3</sup> The resulting motor disability, together with the frequent presence of non-motor features such as depression and cognitive impairment, progressively impacts activities of daily living.<sup>4</sup> In the absence of clinically proven disease-modifying drugs, there is a need for convenient therapies with long-term efficacy in controlling the symptoms of the disease.

## Limitations of current therapy

### Levodopa

Almost 35 years after its introduction, levodopa remains the mainstay of therapy for Parkinson's disease. Levodopa is generally administered orally and is

absorbed in the small bowel. This sometimes presents problems for patients with swallowing difficulties. The short half-life of levodopa necessitates multiple doses, typically commencing with three doses per day and increasing gradually to up to 10 daily doses. Having to take many tablets each day is associated with erratic timing of medication and poor adherence.<sup>5</sup>

Levodopa is routinely administered in combination with a dopa decarboxylase inhibitor, such as carbidopa, to prevent peripheral decarboxylation, improve availability to the central nervous system (CNS) and minimise peripheral dopaminergic side-effects. The catechol-O-methyltransferase (COMT) inhibitors entacapone and tolcapone are used primarily to prevent peripheral breakdown of levodopa and maximise its effect in the CNS. Entacapone can cause diarrhoea,<sup>6</sup> and tolcapone requires extensive liver monitoring and is reserved for severe cases.<sup>7</sup> The COMT inhibitors are therefore used as an adjunct to levodopa only after motor complications begin to emerge. Monoamine oxidase-B inhibitors (MAOBI) also prevent the breakdown of levodopa and dopamine. However, preventing dopamine breakdown through enzyme inhibition (such as with MAOBI) is inherently likely to offer lower efficacy than supplementation with a new substrate (such as with levodopa or dopamine agonists).

Although levodopa is initially effective in Parkinson's disease, motor fluctuations inevitably



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His ongoing clinical and research interests are in Parkinson's disease and movement disorders. He is director of the Regional Movement Disorder Clinic, a co-founder of the Glasgow Movement Disorder Group, and also runs the Regional Dystonia Clinic.

In Parkinson's disease his research is currently focused on diagnostic techniques for Parkinson's disease and therapeutic compliance. Novel approaches to prevention and management of fluctuations and dyskinesia are being explored. These clinical treatment angles reflect his dual training in clinical pharmacology and neurology.

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## Application site: abdomen

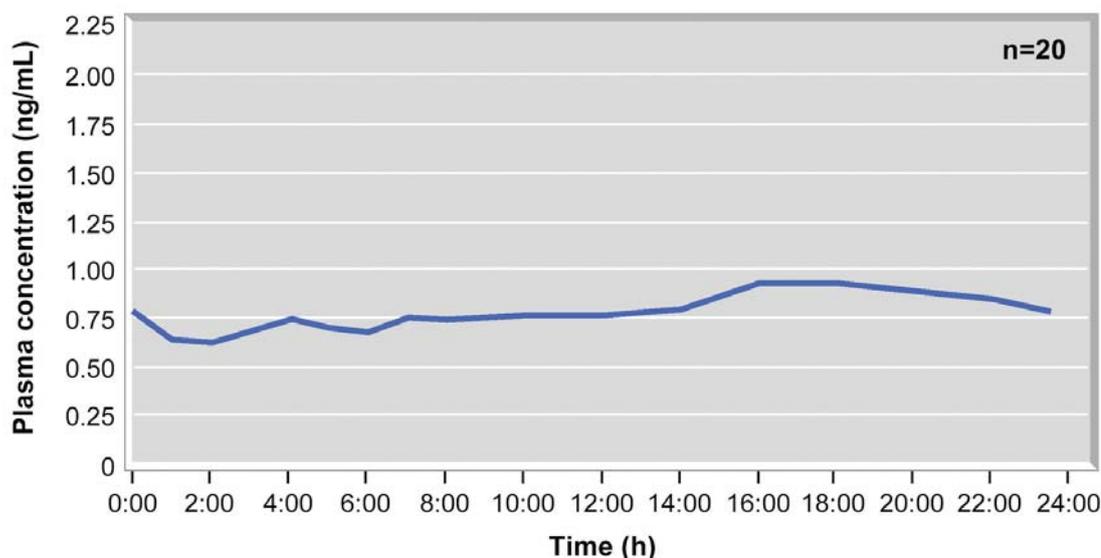


Figure 1: Mean steady-state plasma concentration during repeated daily administration of rotigotine 2mg/24h transdermal patches in patients with early-stage Parkinson's disease. Combined pharmacokinetic data from two days are shown. Data from the abdominal application site are presented; similar profiles were observed for other application sites (shoulder, upper arm, flank, hip, thigh; data presented at the 9th Congress of the European Federation of Neurological Societies, 17-20 September 2005). Reproduced with permission from SCHWARZ PHARMA.

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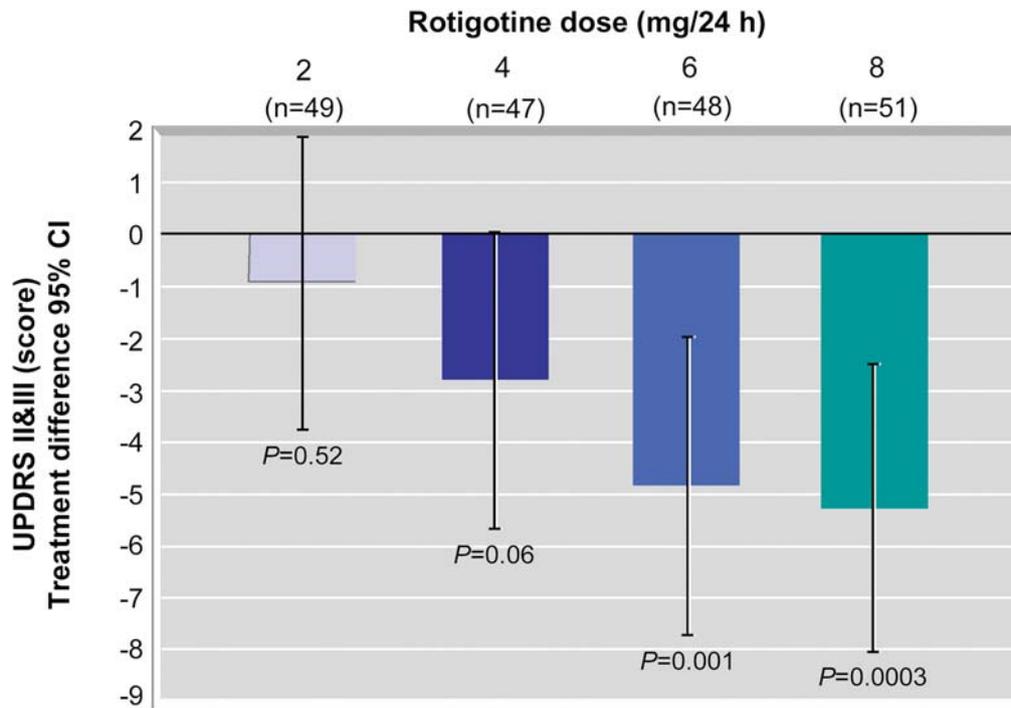


Figure 2: Adjusted treatment difference (difference in mean change between an active treatment group and the placebo group adjusted for the baseline value) for the activities of daily living (part II) and motor (part III) UPDRS scores at week 11 in the phase II trial of rotigotine monotherapy in early-stage Parkinson's disease. Data from the Parkinson Study Group, 2003.<sup>24</sup> Figure reproduced with permission from SCHWARZ PHARMA.

emerge. Motor complications ('wearing off' and 'on-off' fluctuations) typically develop after four to six years of disease duration and affect most patients within 10 years.<sup>8,9</sup> Pulsatile stimulation of dopamine receptors is considered important in this process.<sup>10</sup> There is experimental evidence to suggest that frequent levodopa dosing, in combination with a COMT inhibitor, may reduce pulsatile stimulation and reduce motor fluctuations. For example, in a model of Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), treatment with levodopa plus carbidopa twice or four-times daily produced similar levels of motor fluctuation and dyskinesia.<sup>11</sup> However, co-administration of levodopa and entacapone four-times daily reduced fluctuations and lessened dyskinesia.

#### Dopamine agonists

Dopamine agonists are often used as a first-line treatment option because they delay the onset of motor fluctuations and dyskinesia.<sup>10</sup> Dopamine agonists generally have longer half-lives than levodopa and thus stimulate receptors for longer, reducing peaks and troughs. Nevertheless, many dopamine agonists have half-lives of less than 12 hours, and require multiple daily oral doses. The dopamine agonist cabergoline has a relatively long half-life (>24 hours), but, in common with other ergot-derived agents, is associated with potentially severe fibrotic reactions.<sup>12</sup> To reduce the risk of fibrotic reactions, non-ergot dopamine agonists are preferred.<sup>10</sup>

#### The need for continuous dopaminergic stimulation

In healthy individuals, striatal dopamine receptor activation remains relatively constant.<sup>10</sup> Therapies that provide non-pulsatile continuous dopaminergic stimulation (CDS) may be able to prevent the development of motor complications in early-stage Parkinson's disease, or reverse motor complications if initiated in late-stage disease. Studies with continuous infusion of levodopa or dopamine agonists support

the hypothesis that continuous stimulation reduces the risk of motor complications.<sup>13,14</sup> However, continuous infusion is expensive and impractical for most patients. Sustained-release preparations of levodopa have shown no advantages in terms of postponing or preventing long-term motor complications compared with immediate-release formulations,<sup>15,16</sup> probably because the increase in effective half-life is insufficient to overcome pulsatile stimulation.

#### The rotigotine transdermal patch

Transdermal delivery is a potential solution to providing continuous drug delivery for patients with Parkinson's disease. Rotigotine is a non-ergot, selective D3/D2/D1 dopamine agonist<sup>17</sup> that can be delivered transdermally due to its high lipid solubility. Rotigotine resembles dopamine structurally and has a similar receptor profile, with significant D1 receptor activity. In contrast to ergot-derived dopamine agonists, rotigotine has minimal 5-HT<sub>2B</sub> activity, and therefore has a low risk of inducing fibrosis and cardiac toxicity.<sup>18</sup> Rotigotine also has agonist actions on 5-HT<sub>1A</sub> receptors and antagonist actions on  $\alpha_{2B}$  receptors, which may theoretically contribute to other beneficial effects, such as antidyskinetic activity and antidepressant action,<sup>19,20,21</sup> although this has yet to be evaluated in clinical trials.

The rotigotine transdermal patch contains the drug in a silicone adhesive, which is spread evenly across a foil backing. This configuration provides uniform release of the drug at a constant rate, such that drug delivery is directly proportional to patch size and gives stable plasma drug levels over 24 hours (Figure 1). Microdialysis studies showed that constant plasma levels of rotigotine resulted in constant dopaminergic stimulation (as demonstrated by persistent decreases in extracellular dopamine, which indicate constant stimulation of presynaptic dopamine receptors).<sup>22</sup> Further experimental investigation showed that CDS by rotigotine had a very low propensity to induce dyskinesias.<sup>23</sup>

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### Clinical efficacy in early-stage Parkinson's disease

The rotigotine transdermal patch was evaluated in a randomised, double-blind, placebo-controlled, phase II study of 242 patients with early-stage Parkinson's disease.<sup>24</sup> Patients received patches containing 4.5, 9.0, 13.5 or 18.0mg of rotigotine (equivalent to delivered doses of 2, 4, 6 or 8mg/24h) or placebo for 11 weeks. A dose-dependent improvement in Unified Parkinson's Disease Rating Scale (UPDRS) II and III scores between baseline and week 11 was observed, with the improvement being significant ( $P \leq 0.001$ ) for the 6mg/24h and 8mg/24h dose groups (Figure 2).

These promising results were confirmed in a phase III study of 302 patients with early-stage Parkinson's disease.<sup>25</sup> Patients received an initial dose of rotigotine 2mg/24h (or placebo), which was titrated weekly in 2mg/24h increments to an optimal response or a maximum of 6mg/24h, which was then continued for a further 24 weeks. Patients who received rotigotine had significant improvements in UPDRS II and III scores at the end of treatment (mean improvement of -4.0 points compared with a worsening of +1.3 in the placebo group;  $P < 0.0001$ ), and there was also a significantly greater response rate (percentage of patients with  $\geq 20\%$  reduction from baseline in UPDRS II and III) for patients treated with rotigotine than for patients who received placebo (47.5% vs 18.8%;  $P < 0.0001$ ).

### Safety and tolerability

Adverse events from the rotigotine transdermal patch were similar to those of other dopamine agonists,<sup>26,27</sup> including headache, dizziness, nausea, vomiting and somnolence.

One potential disadvantage of transdermal drug delivery is the potential for application-site reactions. In clinical trials, the rotigotine transdermal patch was associated with an incidence of application-site reactions of 39%<sup>24</sup> and 44%,<sup>25</sup> although only a small subset was severe. This means that a small number of patients are unable to continue using the rotigotine transdermal patch (around 4–5% in clinical trials discontinued because of application-site reactions). The risk of skin reactions is reduced by daily rotation of the application site, and there is evidence of a lower rate of skin reactions when the rotations are strictly undertaken.

### Summary

Rotigotine is the first dopamine agonist to be delivered successfully by transdermal application, and offers a new option for patients with early-stage Parkinson's disease. Continuous drug delivery from transdermal application of rotigotine provides stable plasma drug levels over 24h. This should translate into continuous, non-pulsatile dopaminergic stimulation, which could be beneficial in delaying long-term motor complications.

## Rotigotine is the first dopamine agonist to be delivered successfully by transdermal application, and offers a new option for patients with early-stage Parkinson's disease

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