Expert Opinion

informa
healthcare

Transdermal rotigotine: a new non-ergot dopamine agonist for the treatment of Parkinson's disease

Y Naidu & K Ray Chaudhuri†
†*King's College Hospital, Department of Neurology, 9th Floor Ruskin Wing, Denmark Hill, London, SE5 9RS, UK*

An important conceptual development to avoid the occurrence of motor dyskinesias in Parkinson's disease is continuous dopaminergic stimulation. Studies in animal models and humans suggest that continuous dopaminergic stimulation could be achieved by the infusions of different dopamine agonists or levodopa, and may significantly reduce the risk of dyskinesias associated with treatment strategies utilising pulsatile treatment options. However, so far, these techniques have either necessitated frequent intake of oral therapy or invasive parenteral treatment. The rotigotine transdermal delivery system represents a significant development that allows a constant delivery of a non-ergot dopamine agonist using a once-daily regimen, achieving steady plasma levels. Clinical trials demonstrate the efficacy of rotigotine in early and advanced Parkinson's disease, with important implications for treatment of non-motor symptoms of Parkinson's disease.

Keywords: non-ergot dopamine agonists, Parkinson's disease, transdermal rotigotine

Expert Opin. Drug Deliv. (2007) 4(2):111-118

1. Introduction

Parkinson's disease (PD) was first described by James Parkinson in 1817 and remains one of the most important disabling illnesses of later life. It is estimated to affect 1% of 70-year-olds, but it is also seen in younger people, with 10% of cases occurring before the age of 50 [1,2]. In people with PD, progressive degeneration of the dopamine-producing cells in the substantia nigra (pars compacta) combined with loss in the noradrenergic, cholinergic and serotoninergic nuclei and pathways, produce clinical features that range from the commonly recognised motor symptoms, such as cognitive problems, apathy, depression, anxiety and hallucinations, to non-motor symptoms (NMS), such as sleep disorders, pain, sexual dysfunction and bowel problems [2,3].

Therefore, the treatment of PD needs to be comprehensive, and aim to treat both motor and non-motor symptoms [3]. Strategies to treat the cardinal motor symptoms of PD, such as bradykinesia, tremor and rigidity, have been refined and some NMS, such as depression sleep problems, constipation and bladder problems, can be effectively treated. The cornerstone of treatment of PD remains levodopa (LD) therapy [1,4]. Patients given LD experience a smooth, predictable and lasting response to small amounts of LD during the early years of treatment, but with the progression of PD, treatment-related problems arise [5-7]. These can be summarised as the wearing-off phenomenon and the development of dyskinesias. Dyskinesias are progressive and in ~ 20 – 30% of cases become severe, causing major distress to patients and carers, and significantly increasing the cost of care of PD [5,6].

2. Continuous dopaminergic stimulation

Continuous dopaminergic stimulation (CDS) is a relatively modern concept that has been shown to reduce the severity and incidence of dyskinesias, based on the fact that pulsatile delivery of dopamine to the deafferented dopamine receptors in the striatum is likely to be dyskiensogenic [8,9]. CDS may prevent or reverse motor complications resulting from reduced priming of the basal ganglia for involuntary movements, compared with agents that produce pulsatile stimulation [9]. However, in clinical practice, whether or not CDS is meaningful remains controversial, and some do not accept that CDS is a realistic option in PD. Theoretically, the potential benefits of CDS are many, and may include improvements in aspects of sleep in PD by providing 24-h cover [10].

If it is accepted that CDS is achievable in PD patients, then this can be achieved in various manners, including the parenteral administration of LD preparations or dopamine agonists (Table 1). For example, an open-label study of six patients with PD and severe motor complications, on standard oral LD/carbidopa, demonstrated that continuous daytime intestinal infusions of LD led to significant improvements in both the number of 'off periods' and dyskinesia [9]. A randomised crossover trial in 12 patients with intestinal infusion of carbidopa/LD resulted in increased on-time and reduced off-time, compared with oral sustained-release carbidopa/LD [11]. A retrospective review of 64 patients receiving subcutaneous apomorphine infusion as monotherapy resulted in a mean maximum reduction in dyskinesia severity, frequency and duration [12]. In a prospective study, the improvement of dyskinesias with continuous subcutaneous infusion of apomrophine has been reported [13]. Studies have also suggested an improvement of motor fluctuations in PD with lisuride infusion, compared with pulsatile treatment with oral LD [14].

However, continuous infusion by injections or infusions is expensive, and can be time-consuming and impractical in many patients. Alternatives such as oral sustained-release preparations have shown no advantages in terms of preventing long-term motor complications, compared with immediate-release formulations [15]. The STRIDE (Stalevo Reduction in Dyskinesia Evaluation) study attempts to compare regular dosing of LD combined with entacapone, in an effort to mimic CDS (Stalevo™, Orion Pharma), with conventional LD. The results of the STRIDE study are awaited with interest. Due to the problems of regular oral dosing in PD patients, a transdermal delivery system that provides continuous drug delivery and constant plasma levels should theoretically provide CDS – and is a potentially attractive option for patients with PD [16]. In addition, transdermal administration avoids potential interactions with food, and the drug reaches the site of action without hepatic first-pass metabolism in the liver. Although dismissed by many as a nonissue, recent work indicates that compliance with medication is an issue in the care of PD, and to many patients, transdermal patches (once-daily) may be a more acceptable method of delivering medication [17]. A further advantage is that the patch formulation may be more suitable than oral therapy in a small population of patients with dysphagia or those undergoing surgery.

Table 1. Possible therapeutic strategies for continuous dopaminergic stimulation that can be used in a realistic clinical population of Parkinson's disease patients.

Levodopa based	Non-levodopa based	Surgical
CR levodopa	Cabergoline once- or twice-daily	STN stimulation
CR levodopa + COMT Inhibitor	Apomorphine (s.c.) infusion	Medial pallidum stimulation
CR levodopa + MAO Inhibitor	Lisuride (s.c.) infusion	
Frequent small dosing of oral levodopa	Transcutaneous patch of dopamine agonist (rotigotine, lisuride)	
Levodopa infusion (intraduodenal) (Duodopa)	CR ropinirole	

CR: Controlled-release; COMT: Catechol-*O*-methyl transferase; MAO: Monoamine oxidase; s.c.: Subcutaneous; STN: Subthalamic nucleus.

3. Mechanism of action

Rotigotine is the first and only transdermal patch available that contains a non-ergot, selective $D_1/D_2/D_3$ receptor active dopamine agonist [18]. In animal models, rotigotine administration shows greater locomotor activity in bilaterally lesioned monkeys, compared with quiniprole, pramipexole, ropinirole and cabergoline [19,20]. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated marmosets, continuous administration of rotigotine results in the lowest dyskinesia scores [20]. Rotigotine has a significant similarity to the structure of dopamine (Figure 1) and shares similar receptor affinity (Table 2), suggesting that the response to rotigotine should be of a natural/physiological nature [21,22]. Rotigotine has a broad spectrum of action across the $D_1 - D_5$ receptors. In addition to D_3 activity, rotigotine also has considerable affinity for the D_1 receptor, unlike other dopamine agonists, such as cabergoline, pergolide, pramipexole and ropinirole (Table 3) [22]. This is important because D1 activity is proposed to synergistically enhance the effect mediated via D_2-like receptors [23]. Rotigotine seems to have no affinity for 5-HT_{2b} receptors, which have been implicated in the pathogenesis of ergot dopamine agonists, such as pergolide-related fibrotic side effects and particularly cardiac valvulopathy [24,25]. Recently, this issue

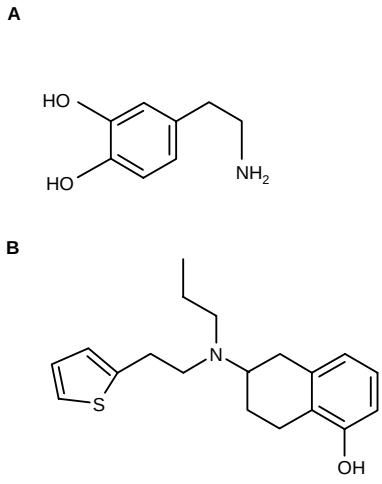

Figure 1. The structures of A. dopamine and B. rotigotine.

has been highlighted in an article focusing on the risks of valvulopathy with cabergoline and pergolide, and further indicates the link of valvulopathy with drugs having a high affinity for 5-HT_{2b} receptors. Therefore, the negligible affinity of rotigotine for 5-HT_{2b} receptors is pharmacologically appealing [26] Rotigotine binds to 5-$HT1_A$ and 5-HT_7, and is an antagonist at α_{2B} receptors. It has been suggested that the action of rotigotine on 5-$HT1_A$ and α_{2B} receptors may contribute to other beneficial effects, such as a possible antidepressant effect (5-HT_{1A} agonistic action) and antidyskinetic action (α_{2B} antagonistic action) [27-29].

In terms of composition, rotigotine is dispersed in a silicone adhesive and then spread evenly across a silicone backing [20]. This permits uniform release of the drug delivery at a constant rate (Figure 2).

4. Clinical trials

Overall, a total of 674 subjects have been evaluated in the Phase I programme of rotigotine development involving 17 clinical Phase I trials [18]. These show that there is continuous drug delivery to the skin, with reproducible absorption and stable 24 h plasma levels. There appears to be no drug accumulation, and rotigotine is eliminated in the urine and faeces, with very low renal excretion [20]. Studies indicate a low drug interaction potential with the CYP450 system, drug transport and plasma protein binding. Dose adjustment in relation to age, gender, moderate hepatic failure and renal failure, including dialysis, is not required.

Phase III trials have enrolled ~ 1200 patients worldwide, and showed that rotigotine provided effective relief from the symptoms of early and advanced PD. The trials included two key Phase III trials in early stage patients with PD, and two Phase III trials in patients with advanced-stage PD.

Table 2. The affinity for dopamine and rotigotine for dopamine receptor subtypes

Dopamine receptor subtype	Dopamine affinity pK_i	Rotigotine affinity pK_i	Affinity ratio (dopamine K_i: rotigotine K_i)
D_1	5.6	7.1	1:28
D_2	6.3	7.9	1:40
D_3	7.6	9.2	1:34
D_4	7.4	7.8	1:3
D_5	6.6	8.3	1:42

Data from [22].

Table 3. Affinity of rotigotine and other dopamine agonists for dopamine receptor subtypes.

Drug	D_1	D_2L	D_3	D_4	D_5
Rotigotine	++	++	++++	++	+++
Cabergoline	+	++++	++++	++	++
Pergolide	+	++	+++	++	++
Pramipexole	•	•	++	+	•

Data from [22].
•: pK_i < 6; +: pK_i 6 – 7; ++: pK_i 7 – 8; +++: pK_i 8 – 9; ++++: pK_i 9 – 10

4.1 Early Parkinson's disease

The Parkinson Study Group carried out a randomised, double-blind, placebo-controlled, trial of untreated PD in 242 patients for 11 weeks [30].

Patches containing 4.5, 9.0, 13.5 and 18 mg of drugs, or placebo, released 2.0, 4.0, 6.0 and 8.0 mg rotigotine, respectively. There was a significant dose-related improvement in motor activities and activities of daily living subscales of the Unified Parkinson's disease Rating Scale (UPDRS) between baseline and week 11, at doses of 6.0 and 8.0 mg, compared with placebo (see Figure 3). Mean changes in the sum of parts II and III of the UPDRS between baseline and week 11 (end of the maintenance period) were -5.07 (6.0-mg group) and -5.30 (8.0-mg group), compared with patients receiving placebo (-0.3; $p < 0.001$).

In an intention-to-treat population, 177 patients received rotigotine (titrated at 2.0 mg/24 h for week 1, 4.0 mg/24 h for week 2, 6.0 mg/24 h for week 3) compared with 96 patients on placebo over a 27-week period [31].

The rotigotine-treated arm showed a significant improvement in UPDRS II and III subscale changes over a 28-week period (see Figure 4). Responder rates (defined as ≥ 20% reduction in UPDRS II and III scores) were significantly higher ($p < 0.0001$) in the rotigotine-treated arm (47.5%) compared with placebo (18.8%). Nausea, headache, vomiting and somnolence were more common in the rotigotine arm. Application site reactions were higher with rotigotine (44%) than placebo (12%).

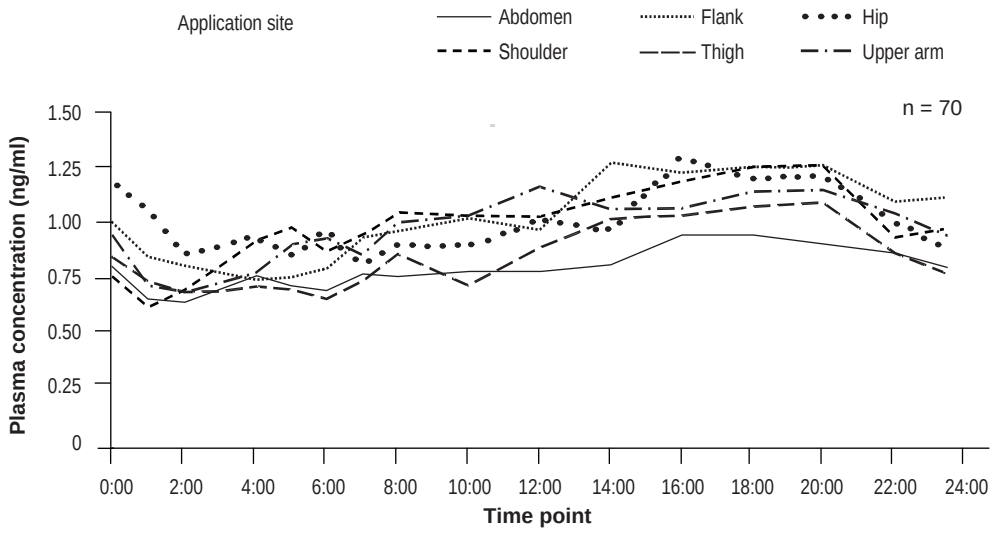

Figure 2. Absorption profile of rotigotine and relationship to application site.
Information from [19,20].

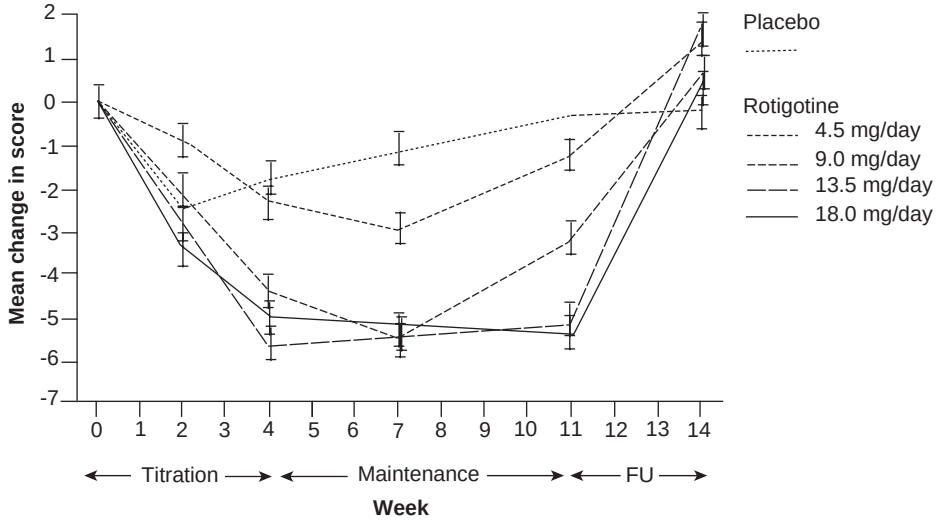

Figure 3. The Effect of Rotigotine on UPDRS score as reported in the trial by the Parkinson Study group.
Rotigotine 4.5 mg/day = 2 mg, 9.0 mg/day = 4 mg/day, 13.5 mg/day = 6 mg/day, 18.0 mg/day = 8 mg/day.
Data from [31].

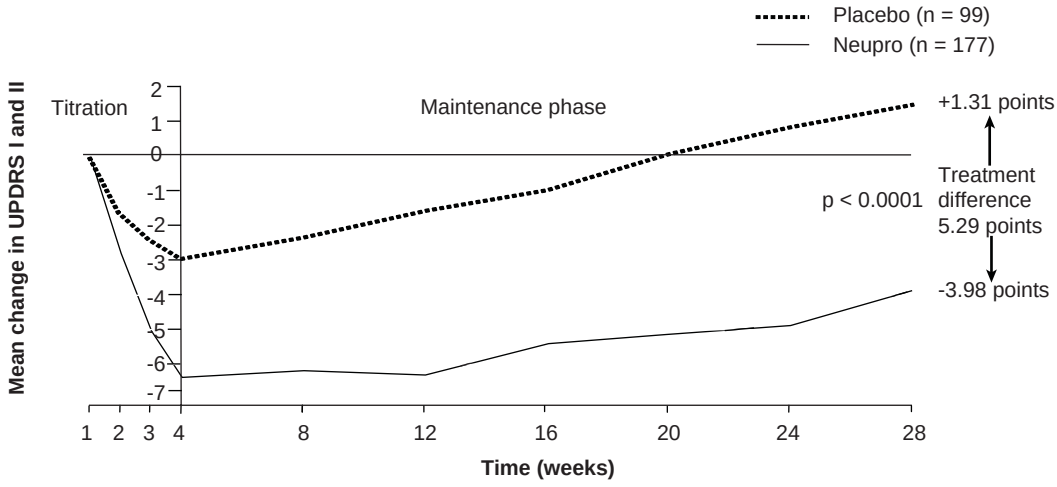

Figure 4. Rotigotine significantly improves UPDRS scores in early Parkinson's disease: Phase III monotherapy placebo-controlled trial.
Data from [31].
UPDRS: Unified Parkinson's disease Rating Scale.

4.2 Advanced Parkinson's disease

A large, multi-centre, randomised, double-blind, placebo-controlled trial [32] was designed to confirm the safety and efficacy of rotigotine in patients with advanced PD (i.e., in combination with LD).

A total of 351 eligible patients were randomly assigned to treatment with patches delivering either 8.0 or 12.0 mg/24 h of rotigotine, or placebo. Patients were titrated to the randomised dose over a 4-week period, and this was followed by a maintenance phase of 24 weeks. There were no relevant differences among the treatment groups in terms of baseline demographics and clinical variables.

The primary efficacy variables in this trial were the change from baseline in absolute off-time, and the responder rate, defined as the proportion of patients showing a decrease in absolute off-time from baseline of ≥ 30%. Both doses of rotigotine showed significantly different decreases from baseline in absolute off-time compared with placebo (1.8 h [$p < 0.0001$] and 1.2 h difference [$p = 0.003$] for 8.0 mg/24 h and 12.0 mg/24 h, respectively), and a significantly greater decrease in absolute off-time from baseline of ≥ 30% (22.2% [$p = 0.001$] and 20.6% [$p = 0.001$] difference for 8.0 mg/24 h and 12.0 mg/24 h, respectively). The decrease in off-time was associated with an increase in 'on without troublesome dyskinesia' time. There was no increase in 'on with troublesome dyskinesia' time. The most common adverse events were application-site reactions, nausea, somnolence and dizziness.

A second Phase III trial in patients with advanced PD was also placebo-controlled and included pramipexole as an active comparator [33].

In this multi-centre, multinational trial, 506 patients were randomised to receive rotigotine, pramipexole or placebo in a ratio of 2:2:1. Patients randomised to receive rotigotine were titrated weekly in 2.0 mg/24 h increments to an optimal response or a maximum dose of 16.0 mg/24 h. Patients randomised to receive pramipexole were titrated weekly to an optimal response or a maximum dose of 4.5 mg/day. The primary efficacy variable was the change from baseline in absolute off-time. Of the patients who entered the trial, 204 were randomly assigned to rotigotine, 201 to pramipexole, and 101 to placebo. The trial arms were well balanced with respect to baseline demographics and clinical variables.

Compared with patients in the placebo group, patients who received either rotigotine or pramipexole had significant decreases in off-time (decrease of 2.44 and 2.82 h for rotigotine and pramipexole, respectively, compared with 0.88 h for placebo; $p < 0.001$). Rotigotine was non-inferior to pramipexole for the reduction in off-time. The rotigotine group had a greater increase in time spent 'on without troublesome dyskinesias' than the other groups. Application-site reactions, nausea and vomiting were the most common adverse events. The incidence of psychiatric adverse events was similar between rotigotine and placebo, but higher with pramipexole [33].

5. Safety and tolerability

Rotigotine is generally well tolerated and a survey of dopamine agonist trials suggested that adverse events are similar to those of other dopamine agonists (see Table 4) [29].

Table 4. An indirect comparison of side effect profile of commonly used dopamine agonists (from monotherapy studies) and rotigotine.

	Incidence (%)			
	Indirect comparisons			
Adverse event	**Rotigotine (n = 649)**	**Ropinirole (n = 179)**	**Pramipexole (n = 151)**	**Cabergoline (n = 208)**
Nausea	38	49	36	37
Vomiting	13	16	NR	37
Somnolence	25	27	32	18
Dizziness	18	20	26	31
Hypotension	1	12	6	31
Headache	14	14	21	NR
Hallucination	2	17	9	5

Data from [29].
NR: Not recorded.

The clinical trials conducted in patients with early PD showed that rotigotine is at least as well tolerated as other dopamine agonists, although it should be noted that these are indirect comparisons, and there are methodological problems in trying to compare rotigotine and other dopamine agonists from separate trials, because of different baseline characteristics and study designs [34].

One 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 reaction of 39 – 44%, although only a small subset had a severe reaction. 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.

Tolerability of overnight switching to rotigotine from other agonists, such as pramipexole, cabergoline and ropinirole, has also been reported in a Phase IIIb open-label, three-arm, multi-centre, multinational study [35]. A total of 50 patients receiving ropinirole (switch equivalent 8.0 – 9.0 mg/day to rotigotine 8.0 mg/24 h), 50 receiving pramipexole (switch equivalent 2 mg [salt] per day to rotigotine 8.0 mg/24 h) and 30 receiving cabergoline (switch equivalent 3 mg/day to rotigotine 8.0 mg/24 h) were switched to rotigotine overnight, which was well tolerated with an improvement in mean UPDRS scores (-1.8). Overall 80.2% needed no further dose adjustments after the initial switch.

6. Conclusions and place in therapy

Rotigotine skin patches represent an important development in the treatment of PD and are especially suitable for PD patients who may be non-compliant with taking their oral medications three or more times a day because of inconvenience or forgetfulness. A particular subset of patients may be young, working patients who may find the concept of using the patch particularly appealing. The non-oral and non-invasive approach, providing at least a theoretical basis for CDS in real life, is attractive to patients and carers, and the authors' own clinical experience suggests that patients are keen on using this drug. In addition, the authors feel that rotigotine patches may provide some important additional advantages to oral treatment strategies, such as:

- The patch may provide a simple therapeutic option in a small number of PD patients who may be acutely ill and unable to take oral treatment (also in the pre/postsurgical period)
- A possible beneficial effect on NMS, such as sleep and restless legs syndrome (RLS), analogous to effects seen with cabergoline and apomorphine [36].
- The advantages of a non-ergot dopamine agonist with no activity at the serotonin 5-HT_{2b} receptor subtype.

Further studies specifically addressing the role of rotigotine skin patches in the management of NMS, such as sleep, RLS and nighttime pain, are required.

7. Expert opinion

Dyskinesias constitute a significant burden for a proportion of people with PD and, in some, become progressive, causing severe disability, substantially increasing the cost of care of PD and requiring invasive treatment strategies, such as deep brain stimulation or apomorphine infusion. Studies in animal models and humans suggest that a key cause of dyskinesia is pulsatile treatment strategies for PD, and CDS is desirable as a modern treatment option. Rotigotine transdermal treatment delivered by a skin patch/24 h provides an useful way of providing CDS, at least theoretically, backed up by robust pharmacokinetic data in PD. Randomised, double-blind clinical trials have now

shown the efficacy of rotigotine compared with placebo, and at least one recent study has suggested that rotigotine is as efficacious as pramipexole in advanced LD treated PD. In addition, there is evidence based on open-label studies that the 24-h effect of rotigotine may help some dopaminergic non-motor symptoms of PD, such as aspects of sleep dysfunction. However, the problem is that, although the notion of using rotigotine is attractive, the efficacy data needs to be somewhat more robust. This may be related to the fact that although much data support the fact that rotigotine appears to be most effective at doses of up to 16.0 mg/24 h, the doses licensed for treatment of early PD were restricted to 8.0 mg/24 h only. Therefore, the recent licensing of rotigotine as adjunctive treatment of PD to doses of up to 16.0 mg/day, is welcome. At a dose of up to 8.0 mg/24 h it is likely that some early PD patients will not derive full benefit from rotigotine due to suboptimal dosing and other agonists, and in comparison may appear stronger in effect. Furthermore, while skin patches may have an initial high uptake in patients, only time will tell if the retention rate of rotigotine is high. Therefore, 'real life' prospective studies addressing tolerability in the young and old PD population is essential. Side effects need to be borne in mind, particularly skin reactions in some susceptible individuals, and the difficulty of applying the patch in hairy subjects. Nevertheless, this is an exciting development in the field of PD and, for the first time, we have data whereby rotigotine has been formally compared with other modern dopamine agonists. This is to be applauded. Another key area of interest is the effort by the manufacturers to develop data related to the treatment of some key non-motor symptoms of PD with rotigotine, for example, aspects of sleep dysfunction. The latter is now recognised by the National Institute for Health and Clinical Excellence as one of the major unmet needs in PD. Although some would argue that dopaminergic tone is low at night and, as such, PD patients may not need 24-h dopaminergic stimulation, clinical experience, overnight dopamine agonist infusion (apomorphine) and deep brain stimulation studies all suggest that dopaminergic nocturnal problems, such as RLS, nocturnal akinesia, nocturnal off-related symptoms, early morning dystonia and even nocturia, can benefit from sustained dopaminergic stimulation throughout the night.

Conflict of interest

KR Chaudhuri has received honoraria for sponsored lectures from GSK, Boehringer Ingelheim, Schwarz, Britannia and Novartis. He also serves on the Schwarz advisory board.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. CLOUGH CG, CHAUDHURI KR, SETHI KD: Parkinson's disease. Health Press, Oxford (2003):7-19.
2. HOEHN MM, YAHR MD: Parkinsonism: onset, progression and mortality. *Neurology* (1967) 17:427-442.
3. CHAUDHURI K R, HEALY D, SCHAPIRA AHV: The non-motor symptoms of Parkinson's disease. Diagnosis and management. *Lancet neurology* (2006) 5:235-245.
   - Useful and extensive review of the impact, diagnosis and assessment of non-motor symptoms of Parkinson's disease.
4. OLANOW CW, WATTS RL, KOLLER WC: An algorithm (decision tree) for the management of Parkinson's disease (2001): Treatment guidelines. *Neurology* (2001) 56(5):S1-S88.
5. MARSDEN CD, PARKES JD: Success and problems of long-term levodopa therapy in Parkinson's disease. *Lancet* (1977) 1:345-349.
6. RAJPUT AH, FENTON ME, BIRDI S *et al.*: Clinical-pathological study of levodopa complications. *Mov. Disord.* (2002) 17:289-296.
7. RASCOL O, GOETZ C, KOLLER W, SIMPATICO C: Treatment interventions for Parkinson's disease: an evidence based assessment. *Lancet* (2002) 359:1589-1598.
8. OLANOW W, SCHAPIRA AH, RASCOL O: Continuous dopamine-receptor stimulation in early Parkinson's Disease. *Trends Neurosci.* (2000) 23: S117-126.
   - An evidence based resource for the clinical application of the concept of continuous dopaminergic stimulation.
9. STOCCHI F, VACCA L, RUGGIERI S *et al.*: Intermittent vs. continuous levodopa administration in patients with advanced Parkinson's disease; a clinical and pharmacokinetic study. *Arch. Neurol.* (2005) 62:905-910.
10. DHAWAN V, HEALY D, PAL S, CHAUDHURI KR: The sleep related problems of Parkinson's disease. *Age Ageing* (2006) 35:220-228.
    - A recent and up-to-date review of sleep problems in Parkinson's disease.
11. NYHOLM D, ASKMARK H, GOMES-TROLIN C *et al.*: Optimising Levodopa pharmacokinetics: Intestinal infusion versus oral sustained –release tablets. *Clin. Neuropharmacol.* (2003) 26(3):156-163.
12. MANSON AJ, TURNER K, LEES AJ: Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow up study of 64 patients. *Mov. Disord.* (2002) 17(6):1235-1241.
13. KATZENSCHLAGER R, HUGHES A, EVANS A *et al.*: Continuous subcutaneous apomorphine therapy improves dyskinesias in PD: a prospective study using single –dose challenges. *Mov. Disord.* (2005) 20:151-157.
    - Important study of the role of apomrophine continuous infusion.
14. OBESO JA, LUQUIN MR, MARTINEZ-LAGE JM: Lisuride infusion pump: a device for the treatment of motor fluctuations in Parkinson's disease. *Lancet* (1986) 1:467-470.
15. KOLLER WC, HUTTON JT, TOLOSA E *et al.*: Immediate –release and controlled release carbidopa/levodopa in PD: a 5-year

randomized multicenter study. Carbidopa/Levodopa study Group. *Neurology* (1999) 53:1012-1019.

16. RASCOL O:Transdermal delivery of dopaminergic agents. *Neurology* (2005) 65(1): S1- S2.
17. GROSSET KA, BONE I, GROSSET DG: Suboptimal medication adherence in Parkinson's disease. *Mov. Disord.* (2005) 20:1502-1507.
18. GROSSET D: The rotigotine transdermal patch may provide continuous dopaminergic stimulation in Early- stage Parkinson's disease. *Adv. Clin. Neurol. Rehab.* (2006) 6(2):32-34.
19. JENNER P: A novel dopamine agonist for the transdermal treatment of Parkinson's disease. *Neurology* (2005) 65(1) S3 –S5.
- Clinical application of the concept of continuous dopaminergic stimulation.
20. HEINDL M, SCHELLER D, LEBSANFT K *et al*.: Continuous versus discontinuous administration of rotigotine in a rat model of dyskinesias. *Parkinsonis and Related Disorders* (2005) 11(2): PS002-PS006.
21. POEWE W, LUESSI F: Clinical studies with transdermal rotigotine in early Parkinson's Disease. *Neurology* (2005) 659(1): S11-S14.
22. ROTIGOTINE (NEUPRO) Summary of product characteristics. Schwarz Pharma.
23. PAUL ML, GRAYBIEL AM, DAVID JC *et al*.: D1-like and D2-like dopamine receptors synergistically activate rotation and c-fos expression in the dopamine-depleted striatum in a rat model of Parkinson's disease. *Journal of Neuroscience* (1992) 12:3729-3742.
- An useful paper relating to basal ganlia dopaminergc receptor profile.
24. HORVATH J, FROSS RD, KLEINER-FISMAN G *et al*.: Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. *Mov. Disord.* (2004) 19:656-662.
25. HOROWSKI R, JAHNICHEN S, PERTZ HH: Fibrotic valvular heart disease is not related to chemical class but to biological function; 5-HT2B receptor activation plays crucial role. *Mov. Disord.* (2004) 19:1523-1524.
26. BARA-JIMENEZ W, BIBBIANI F, MORRIS MJ *et al*.: Effects of serotonin 5-HT1A receptor agonist in advanced Parkinson's disease. *Mov. Disord.* (2005) 20:932-936.
27. TOMIYAMA M, KIMURA T, MAEDA T *et al*.: serotonin 5-HT1A receptor agonist prevents behavioral sensitization to L-DOPA in a rodent model of PD. *Neurosci. Res.* (2005) 52:185-194.
28. SRINIVASAN J, SCHMIDT WJ: Treatment with alpha2 –adrenoceptor antagonists, 2 methoxy idazaoxan, protects 6- hydroxydopamine induced Parkinsonian symptoms in rats: neurochemical and behavioral evidence. *Behav. Brain Res.* (2004) 154:353-363.
29. MUCKE HA: Rotigotine. *Schwarz Pharma. Drugs* (2003) 6:894-899.
30. THE PARKINSON STUDY GROUP: A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch. Neurol.* (2003) 60:1721-1728.
31. WATTS RL, WENDT RL, NAUSIEDA B: Efficacy, safety and tolerability of the rotigotine patch in patients with early stage idiopathic Parkinson's Disease: multicentre, multinational, randomized, double blinded placebo controlled trial. *Mov. Disord.* (2004) 19(9): S258.
32. LEWITT PA, CHANG FL, Rotigotine transdermal system in treatment of patients with advanced stage Parkinson's disease. *Eur. J. Neurol.* (2005) 12(Suppl. 2):15 (SC 115) Abstract.
33. POEWE W, GILADI N, MAGUIRE D, BOROOJERDI B: Rotigotine transdermal patch in patients with Parkinson's Disease and motor fluctuations. 24h symptom control in a placebo- and pramipexole-controlled, randomized, doubleblind, double dummy trial *Eur. J. Neurol.* (2006) 13(Suppl. 2): 74(P1126) Abstract.
34. JANKOVIC JJ: Therapeutic strategies in Parkinson's disease. In: *Parkinson's disease and movement disorders.* Jankovic JJ, Tolosa E (Eds) Lippincott Williams & Wilkins, Philadelphia (2002):116-151.
35. LEWITT PA, POEWE W, RASCOL O, GILADI N, PATTON J. Overnight switch from ropinirole, pramipexole and cabergoline to rotigotine transdermal patch. *Eur. J. Neurol*. (2006) 13(Suppl. 2):321 SAT8-3.
36. STIASNY-KOLSTER K, KOHNEN R, SCHOLLMAYER E *et al*.: The Rotigotine Sp 666 Study Group. Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. *Mov. Disord.* (2004) 19:1432-1438.

Affiliation

Y Naidu[1] BSc RGN & K Ray Chaudhuri[†1,2,3,4] MD FRCP DSc
[†]Author for correspondence
[1]Research Nurse and Co-ordinator, University Hospital Lewisham, National Parkinson Foundation Centre of Excellence and Regional Movement Disorders Unit, UK
[2]Consultant Neurologist and Co-Director, King's College Hospital, National Parkinson Foundation Centre of Excellence and Regional Movement Disorders Unit, UK
[3]King's College, London, Guy's, King's & St Thomas' School of Biomedical Medicine, UK
[4]King's College Hospital, Department of Neurology, 9th Floor Ruskin Wing, Denmark Hill, London, SE5 9RS, UK
Tel: 0208 333 3030 6184;
Fax: 0208 333 3093;
E-mail: Ray.chaudhuri@uhl.nhs.uk