Expert Opinion

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Rotigotine transdermal delivery for the treatment of Parkinson's disease

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Background: Rotigotine is a non-ergot dopamine agonist that has been developed as a new transdermal formulation, and is indicated for use in early (USA and Europe) and advanced (Europe only) Parkinson's disease (PD). The potential advantages of the rotigotine patch include immediacy of effect onset as intestinal absorption in unneeded, constant drug delivery, and ease of use via application of a once-daily adhesive patch. An interesting element of this profile is constant drug delivery, which may avoid pulsatile dopaminergic stimulation, which has been postulated to be related to the development of motor complications. *Objective*: To consider the evidence surrounding the profile of rotigotine and, in particular, whether its constant delivery system offers significant benefits to the treatment of early and advanced PD. *Methods*: Source material was identified using a PubMed search for the term 'rotigotine' (up to March 2008). The review focuses only on publications related to the rotigotine indication for PD. *Results/conclusion*: The rotigotine transdermal patch demonstrates clinical efficacy, alongside a tolerability profile that appears to be well within the range of that observed with other non-ergot dopamine agonists. The once-daily patch formulation may favour compliance but, in similarity with the other theoretical advantages of constant drug delivery (for example reduced emergence of motor complications, improved tolerance to peripheral AEs), requires further detailed study.

Keywords: continuous delivery system (CDS), dopamine agonist, levodopa, motor fluctuations, Parkinson's disease, rotigotine, transdermal patch

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1. Introduction

Parkinson's disease (PD) is a condition that affects every race and culture. In total, approximately 90% of people with PD are diagnosed after the age of 50, with the condition having a worldwide prevalence of 1.6% in the over-65 age group [1].

In common with many other disease areas, the unmet needs for PD therapy comprise improved efficacy, tolerability and ease of drug use/compliance. Levodopa remains the most effective treatment for the motor symptoms of the disease, but it can produce motor complications – such as fluctuations and dyskinesias – after approximately 5 years of therapy. This fluctuating response is thought to be caused by many factors, including the pulsatile dopaminergic stimulation of neurons due to the multiple daily dosing required by levodopa (and many other anti-Parkinsonian drugs). Therefore, within the general unmet need of 'improved efficacy', there is a requirement for a medication that provides an even supply of active drug throughout the day – a 'continuous delivery system' (CDS). In addition, according to one study, over 50% of PD patients miss at least one

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dose of medication per week, and approximately 20% of patients miss three or more doses per week [2]. In this setting, a long-acting CDS would potentially offer a simpler dosing system, promoting patient compliance and resulting in more consistent symptomatic effects.

2. Overview of the current Parkinson's disease market

The majority of drugs available at present for the treatment of PD are taken orally. Oral administration offers convenience, but the subsequent processing via the gastrointestinal system and first-pass hepatic metabolism can make the response, and therefore the dose schedule, difficult to optimize. In addition, many of these drugs require frequent dosing owing to short duration of action and thereby promote pulsatile dopaminergic stimulation of neurones. Various drug delivery strategies have been used to target this problem, including controlled-release oral formulations, drug-combination tablets, fast-acting buccally absorbed tablets, parentally administered drugs, transdermal formulations, and drug delivery direct to the lower gastrointestinal tract (for review, see [3]).

The anti-Parkinsonian, dopamine agonist drug class currently comprises eight marketed agents (ergot and non-ergot agonists) – half of these fall into the 'oral/frequent dose' category described above. The exceptions include cabergoline – which has a half-life of ~ 65 h, allowing once-daily dosing [4], but which may be associated with ergolinic side effects [5] – and apomorphine – which can be given sub-cutaneously, but its complex administration limits its widespread use [6]. An oral, once-daily, extended-release formulation of ropinirole (ropinirole CR) has also been approved for use in PD patients, and an extended-release formulation of pramipexole is in development. Transdermal administration is another option that is currently approved for rotigotine and under investigated for other dopamine agonist, such as lisuride. Continuous drug delivery, such as that provided by transdermal systems, can generate steady-state drug plasma levels [7]. In turn, these steady-state levels have been shown to produce constant receptor stimulation [8], which may help to reduce/delay the occurrence of motor complications in PD, as shown in animal models [9]. However, clinical translation of this theoretical advantage has not yet been fully addressed. Nonetheless, with the recent approval of the rotigotine transdermal patch, this administration route opens up further possibilities for the treatment of PD and for the study of the clinical advantages of dopaminergic CDS application.

3. Introduction to rotigotine

Rotigotine is a new, non-ergot, dopamine agonist that also has 5-HT_{1A} agonistic and α-2-adrenergic antagonistic properties [10,11]. As will be described later in this review, rotigotine is a potent dopamine agonist with the potential for a long-duration effect if administered via the transdermal route [11]. A high lipid solubility makes rotigotine a suitable candidate for transdermal administration [12], while also avoiding the extensive gastrointestinal metabolism that makes rotigotine inappropriate for oral dosing [13]. Consequently, a rotigotine slow-release formulation was developed as a skin 'patch', with the aim of offering continuous drug delivery for patients with idiopathic PD.

Although lisuride is also being tested for transdermal administration in PD [14], rotigotine (marketed as Neupro®) is the first transdermal medication to be approved by the regulatory authorities for use in all stages of PD in Europe [15], and for early-stage PD in the USA [16]. Application to the FDA for approval of the rotigotine patch for use in advanced PD was made during 2007 [17]. The rotigotine transdermal patch was launched onto the European market in March 2006, and onto the US market in July 2007 [16,18]. In 2008, drug stability problems (crystal formation in the patches), which compromised bioavailability, prompted EMEA (European medicines agency) to solicit changes to storage conditions, while FDA asked professionals and patients to recall Neupro® in patients already on treatment and not to initiate any new patients. In addition to its indication as monotherapy and adjunct therapy for PD, rotigotine is in clinical trials for the treatment of restless legs syndrome (RLS) [19,20].

In the treatment of PD, rotigotine is administered once-daily as an adhesive patch, which remains on the skin for a full 24 h before being replaced by another patch at a different site of application [21]. This once-daily administration has the potential to convey valuable patient benefits in terms of convenience and, consequently, compliance. In more advanced patients, these practical benefits could extend to minimizing issues of pill burden and dysphagia (for a specific example, see [22]).

Rotigotine drug delivery has been shown to be proportional to patch size [23], and patches releasing 2 mg (10 cm^2), 4 mg (20 cm^2), 6 mg (30 cm^2), and 8 mg (40 cm^2) of rotigotine per 24 h are now available [21]. For patients with early-stage PD, an initial dose of 2 mg/24 h can be increased in weekly increments of 2 mg/24 h to a maximum dose of 8 mg/24 h, if required [21]. For patients with advanced-stage PD and motor fluctuations, an initial dose of 4 mg/24 h can be increased weekly by 2 mg/24 h to a maximum of 16 mg/24 h, if required [21]. For doses over 8 mg/24 h, multiple patches must be applied [21]. Dose adjustment due to age, gender, weight, or mild to moderate renal or hepatic impairment, is not necessary [21].

4. Chemistry

Rotigotine is the (-)-enantiomer of the aminotetralin derivative, 2-(*N*-propyl-*N*-2-thienylethylamino)-5-hydroxytetralin [11]. It has a structural similarity to dopamine (**Figure 1**),

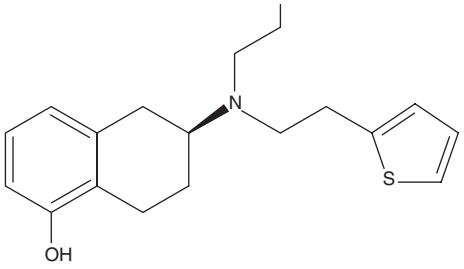

Figure 1. The structure of rotigotine.

and its activity as a dopamine agonist has been shown to be superior (even antagonistic) to that of its (+)-enantiomer [11,24].

For clinical use, rotigotine is supplied as an adhesive patch constructed of three layers (**Figure 2**). The active drug is dissolved in a silicone adhesive (forming the drug-loaded matrix), which is evenly spread onto a siliconized and aluminized polyester backing film, and covered with a release liner that is peeled off prior to application [21]. Other chemical components of the self-adhesive matrix are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidone K90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL-α-tocopherol (E307) [21]. Upon application, rotigotine is absorbed through the skin via transcellular, intercellular (lipophilic), follicular (hydrophilic), and eccrine (hydrophilic) routes [12]. The patches designed to release 2, 4, 6 and 8 mg rotigotine per 24 h, contain 4.5, 9.0, 13.5 and 18.0 mg of rotigotine, respectively [21].

The development of crystals has been noted on some rotigotine patches, and is said to result from the current manufacturing process [25]. Such crystal-related change can, theoretically, modify the efficacy profile because of reduced bioavailability. However, because refrigerated storage of the patches can substantially reduce the development of crystals, EMEA has recently approved the UCB (Union Chimique Belge) submission of a full cold-chain storage and distribution system implementation in Europe – including refrigerated storage by patients [21,25]. In line with this, UCB is replacing all current stocks of the rotigotine patches, and has asked physicians not to initiate any new patients on the patches while supply to existing patients is prioritized [25]. On the contrary, marketing suspension in the USA remains unchanged up to the present time.

5. Preclinical pharmacology

5.1 Preclinical pharmacodynamics

5.1.1 Selectivity

Rotigotine's activity as a dopamine receptor agonist has been demonstrated in several preclinical studies. Rotigotine produced a significant reduction in palatable food consumption (considered to be related to post-synaptic dopamine receptors) in rats, and this effect was countered by the action of a D_2-receptor antagonist [24]. In the same investigation, rotigotine stimulated the yawning response, and this effect was prevented by a dopamine autoreceptor-antagonist [24]. This dopamine receptor agonistic activity was not demonstrated to the same extent by rotigotine's opposing (+)-enantiomer [24].

Rotigotine has agonistic activity at all dopamine receptor subtypes (D_1 – D_5), but demonstrates its highest affinity for the D_3-receptor [11]. *In vitro* profiling using recombinant human receptors revealed that the affinity of rotigotine for the D_3-receptor was approximately 20-fold and 100-fold greater than its affinity for the D_2- and D_1-receptors, respectively [11] – a profile consistent with that of other, earlier, investigations [10,26]. Chase *et al*. Reported K_i values of 0.94 nM (D_3), 11 nM (D_2), and 364 nM (D_1) [26]. Therefore, rotigotine has a ratio of affinity similar to that of dopamine itself, with a preference for the $D_3/D_2/D_1$-receptors – the three major dopamine receptor subtypes expressed in the striatum [23,26]. Compared with pramipexole (K_i values of 8.5 nM for D_3; 616 nM for D_2; and > 50000 nM for D_1) and ropinirole (K_i values of 61 nM for D_3; 970 nM for D_2; and > 50000 nM for D_1), rotigotine shows a higher affinity and similar selectivity for D_2-like dopamine receptor subtypes [27].

In addition, rotigotine acts as an antagonist at the α-2-adrenergic receptor, and as an agonist at the $5HT_{1A}$-receptor [10,11]. *In vitro* functional assays also demonstrate its inhibition of dopamine uptake and prolactin secretion [10]. There is some speculation that relative affinities for the different dopamine receptor subtypes may produce particular anti-Parkinsonian activity [26], but the exact translation of these effects is, as yet, unknown [11].

In addition to selectivity, a slow-release form of rotigotine generated constant extracellular drug levels in the brains of freely moving rats following subcutaneous administration [8]. These levels were maintained for at least 48 h and were accompanied by a concomitant and maintained reduction in extracellular dopamine to about 20% of vehicle control levels [8]. As dopamine synthesis is controlled by presynaptic receptors, this observation supports rotigotine's potential to induce continuous stimulation of dopamine receptors [8].

5.1.2. Effects in animal models of Parkinson's disease

Rotigotine has demonstrated benefits in several animal models of PD. In 6-OHDA lesioned rats, subcutaneous rotigotine induced dose-dependent contralateral turning behaviour [10]. In addition to this, in a study of hemi-Parkinsonian (MPTP-induced) monkeys, intramuscular rotigotine also induced contralateral turning behaviour, as well as exploratory activity and contralateral limb usage [10]. Dose-dependent improvements in motor and non-motor tasks were reported in another study in monkeys, with administration of a D_1-receptor antagonist blocking these motor improvements [28]. In the MPTP-lesioned common

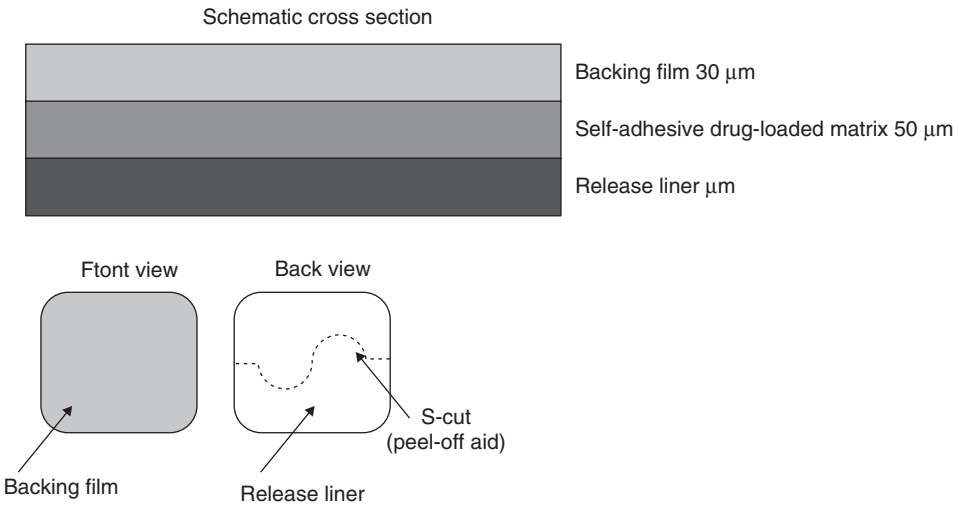

Figure 2. Structure of the rotigotine transdermal patch.

marmoset, subcutaneous rotigotine produced a dose-dependent increase in well-coordinated locomotor activity, with a concomitant reduction in disability scores [29]. This was observed at even the lowest dose of rotigotine (0.019 mg/kg) [29].

With the aim of investigating the induction of dyskinesia, pulsatile administration of rotigotine or levodopa was compared with continuous delivery of rotigotine in 6-OHDA lesioned rats [30]. Discontinuous delivery of rotigotine and levodopa produced increased sensitization of locomotor activity to approximately the same extent, whereas continuous delivery of rotigotine did not produce this sensitization [30]. These initial observations may indicate a lower risk of dyskinesias with continuous drug administration. In a separate investigation, it was noted that high doses of rotigotine produced hyperactivity and restlessness in hemi-Parkinsonian monkeys [30].

5.1.3 *Neuroprotection*

Preliminary evidence indicates that subcutaneous injection of slow-release rotigotine (3 mg/kg) prevents degeneration of neurones in MPTP-treated mice [31]. In addition, further evidence for the potential neuroprotective action of rotigotine comes from an imaging study done in an MPTP-treated macaque model of progressive PD [32]. Using *ex vivo* DAT labelling, the study found that the reduction in Parkinsonian symptoms observed in rotigotine-treated animals correlated with a partial protection of dopamine terminals, although this protection could not be detected by conventional imaging techniques (SPECT) [32]. Nonetheless, these results should be interpreted cautiously, as a number of limitations to the assessment of putative neuroprotective effects by radiotracers have been reported [33]. Additionally, it is often the case that animal evidence of neuroprotection is not confirmed in clinical trials [34].

5.1.4 *Toxicology*

In a 3-month study in albino rats, retinal degeneration was observed by transmission microscopy at a rotigotine dose equivalent to 2.8 times the maximum recommended human dose [21]. However, retinal degeneration was not observed during routine histopathological observation in any species, and the relevance of these findings to humans is not known [21].

In carcinogenicity studies, malignant uterine tumours (in mid- to high-dose female rats) and Leydig cell tumours and hyperplasia (in male rats) were assessed as not relevant to man [21].

Rotigotine has no effect on fertility in male rats, but clearly reduces fertility in female rats and mice owing to an influence on prolactin levels, which are particularly significant in rodents [21]. Rotigotine was found to be embryotoxic in rats and mice at maternotoxic doses [21].

5.2 Preclinical pharmacokinetics

An investigation in rats found that rotigotine undergoes extensive metabolism in the gastrointestinal mucosa, with less than 1% of the dose reaching the liver following intragastric administration [13]. This confirms the poor oral bioavailability of rotigotine. The two major routes for rotigotine metabolism are conjugation (5-*O*-glucuronidation, *N*-depropylation), and *N*-dealkylation by the cytochrome P450 system followed by conjugation (5-*O*-glucuronidation) [35,36]. *N*-dealkylation is performed by multiple CYP450 isoenzymes [35]. Incubation of rotigotine with selective CYP450 inhibitors *in vitro* did not result in extensive inhibition of metabolite production, and further to this, rotigotine showed no effects on CYP450 enzyme activity during *in vitro* and *in vivo* investigations [35]. These results indicate that rotigotine has a low risk of drug–drug interactions related to

CYP450-dependent metabolism [35]. The level of rotigotine plasma protein binding is 92% *in vitro* [21].

6 Clinical pharmacology

6.1 Clinical pharmacokinetics

In a study of eight healthy volunteers, single-dose pharmacokinetics were examined following administration of a 4.5-mg (2 mg/24 h) rotigotine patch, applied for a period of 24 h [23,37]. A median C_{max} of 0.215 ng/ml was observed at 16 h after administration (t_{max}), with an AUC_{0-tz} value of 3.94 ng.h/ml [23,37]. Following patch removal at 24 h, the rotigotine plasma concentration decreased with a median terminal elimination half-life of 6.82 h [23]. These pharmacokinetic values were not markedly affected by mild or severe renal impairment [37]. The pharmacokinetics of rotigotine have not been investigated in patients with severe hepatic impairment [21].

Pharmacokinetic values were also obtained in an open-label study of 63 patients with early PD [38]. Patients received a daily rotigotine dose of 18.0 mg (8 mg/24 h patch delivery, up-titrated from 4.5 mg (2 mg/24 h), in 4.5 mg increments every 6 days) as a once-daily application, which produced a stable mean plasma concentration profile over 24 h [38]. Patch application sites were switched daily, with a mean (± SD) plasma concentration of 0.79 – 0.37 ng/ml for the abdomen patch – a value unaffected by age (< 65 years, ≥ 65 years), site of application or gender [38]. Nonetheless, the absolute bioavailability of rotigotine, which is approximately 37%, can vary from day to day depending on the site of application – from 1% (hip vs abdomen) to 41% (shoulder vs thigh) [21]. The fact that plasma levels remained stable in the aforementioned study [38] and during a 24-week treatment period in a clinical trial [39], further indicates that bioavailability variability may lack of major clinical implications; but this requires further exploration. Rotigotine levels increased proportionally to dose administered [39,40].

The rotigotine volume of distribution in humans is 84 L/kg and, owing to the transdermal administration route, food and/or gastrointestinal conditions are not expected to influence the pharmacokinetics of rotigotine [21]. The majority of the rotigotine dose is excreted in the urine (71%), with approximately 23% excreted in the faeces [21].

Much of these data, though presented at international meetings, has never been published in peer-reviewed journals. Nonetheless, they are publicly available at the FDA website, as they were part of the new drug application (NDA) dossier [41].

6.2 Drug–drug interactions

Further to preclinical data indicating a low risk of drug–drug interactions (described earlier), a study administering a 9.0 mg (4 mg/24 h) rotigotine patch to 12 healthy volunteers showed that rotigotine steady-state pharmacokinetics were not altered upon coadministration with the non-specific CYP inhibitor cimetidine (400 mg bid) [35]. Another study observed pharmacokinetics in 24 patients treated with rotigotine (9.0 mg patch; 4 mg/24 h) with or without concomitant levodopa/carbidopa (100 mg/25 mg bid) for RLS [42]. Concentration–time profiles for rotigotine and for levodopa/carbidopa were unaffected by their use as single or combined therapies, indicating no pharmacokinetic interactions between these drugs [42]. However, as with other dopamine agonists, when given concomitantly, rotigotine may potentiate the adverse reactions of levodopa, including the exacerbation of pre-existing dyskinesia [21].

Coadministration with dopamine antagonists would be expected to diminish rotigotine's effects, and is therefore not recommended [21].

7. Clinical trials in Parkinson's disease patients

7.1 Efficacy

Currently published rotigotine clinical studies include three large-scale Phase III studies in early PD, two large-scale Phase III studies in advanced PD, and two smaller Phase II trials in early and advanced PD. Clinical data from these studies, as well as other investigations that are only available at present as published abstracts, are discussed in the following sections, with study designs summarized in **Table 1**.

In addition to the studies listed in **Table 1**, data from preliminary clinical studies of earlier formulations of rotigotine are also available. A study by Calabrese *et al.* assessed nine patients with moderate to severe Parkinsonism, who received rotigotine as a continuous intravenous infusion over a period of 4.5 h [52]. The authors reported an improvement on the modified Columbia rating scale (MCRS) of 27 – 95%, with maximal response at infusion rates of 2 – 16 µg/kg/h, and rapid initiation/cessation of drug effect upon initiation/cessation of infusion [52]. A placebo-controlled Phase II trial in 82 PD patients examined the efficacy of four doses of an early rotigotine patch formulation, as adjunct to levodopa, over 21 days [53]. The levodopa dose was significantly reduced (primary outcome measure) in patients receiving the two highest rotigotine doses (33.5 mg and 67.0 mg; note that transdermal absorption was less efficient with this earlier formulation) versus placebo, with symptom control maintained despite the reduction in levodopa dose [12,53].

7.1.1 Monotherapy in early PD – symptom control

A Phase II dose-escalation study of rotigotine monotherapy in early PD examined symptom control as a secondary variable [43]. Rotigotine treatment produced a significant improvement in UPDRS (unified Parkinson's disease rating scale)-mental (- 0.41; p = 0.0078), -ADL (activities of daily living; - 2.76; p = 0.0001), and -Motor (- 4.62; p < 0.0001)

Table 1. Summary of rotigotine clinical studies [39,40,43-51].

Study	Design	Duration*	Rotigotine therapy‡	No. of patients	Primary outcome	Principal secondary outcomes
Monotherapy for early PD						
Güldenpfennig *et al.*, 2005 (Phase II)	Dose-escalation, open-label, multicentre	4 weeks	Maximum tolerated dose (≤ 8 mg/24 h)	31	Safety	Tolerability; UPDRS-Mental, -ADL, and -Motor subscores
Parkinson Study Group, 2003 (Phase III)	Randomized, double-blind, multicentre, placebo-controlled	11 weeks	2, 4, 6, or 8 mg/24 h	242	UPDRS-ADL/-Motor subscore	UPDRS-Mental, -ADL, and -Motor subscores; Hoehn and Yahr stage
Watts *et al.*, 2007; Jankovic *et al.*, 2007 (Phase III)	Randomized, double-blind, multicentre, placebo-controlled	27 weeks	Optimal dose (≤ 6 mg/24 h)	277	UPDRS-ADL/-Motor subscore; responder rate	Quality of life (UPDRS; EQ-5D); compliance; safety
Giladi *et al.*, 2007 (Phase III)	Randomized, double-blind, multicentre, placebo-controlled	≤ 37 weeks	Optimal dose (≤ 8 mg/24 h) (ropinirole optimal dose ≤ 24 mg/day)	561	Responder rate	UPDRS-ADL/-Motor subscore; non-inferiority to ropinirole
Adjunct therapy for advanced PD						
Quinn *et al.*, 2001 (Phase II)	Randomized, double-blind, multicentre, placebo-controlled	12 weeks	4, 8 or 12 mg/24 h	324	Safety and dose–response	Total daily OFF time
Verhagen Metman *et al.*, 2001 (Phase II)	Dose-escalation, double-blind	4 weeks	Maximum tolerated dose (≤ 16 mg/24 h)	7	Levodopa dose	UPDRS-Motor score without levodopa; total daily ON/OFF time
Babic *et al.*, 2006; Babic *et al.*, 2004 (Phase II)	Dose-escalation, randomized, open-label	12 weeks + 4-day dose de escalation	Maximum achievable dose (target dose 24 mg/24 h)	34	Tolerability	Total daily ON/OFF time; UPDRS-Total score
LeWitt *et al.*, 2007 – PREFER Study (Phase III)	Randomized, double-blind, multicentre, placebo-controlled	29 weeks	8 or 12 mg/24 h target dose	351	Total daily OFF time; responder rate	Daily ON time; number of OFF periods; UPDRS-ADL, -Motor, and -Complications subscores; safety and tolerability
Poewe *et al.*, 2007 – CLEOPATRA-PD Study (Phase III)	Randomized, double-blind, multicentre, placebo-controlled	6 months	Optimal dose (≤ 16 mg/24 h) (pramipexole 4.5 mg/day)	506	Total daily OFF time; responder rate	Daily ON time; number of OFF periods; UPDRS-ADL and -Motor subscores; safety

*Including titration phase; ‡2 mg/24 h patch = 4.5 mg drug content; 4 mg/24 h patch = 9.0 mg drug content; 6 mg/24 h patch = 13.5 mg drug content; 8 mg/24 h patch = 18.0 mg drug content; 12 mg/24 h patch = 27.0 mg drug content; 16 mg/24 h patch = 36.0 mg drug content; 24 mg/24 h patch = 54.0 mg drug content)

UPDRS-Unified Parkinson's disease rating scale; ADL-Activities of daily living.

subscores, compared with baseline values [43]. The majority of patients (83%) were maintained at a rotigotine dose of 8 mg/24 h – the maximum dose allowed in this study [43]. Although providing an indication of efficacy, this small-scale trial was not placebo-controlled, and safety was the only primary outcome measure [43].

However, three large-scale, placebo-controlled Phase III studies of rotigotine in early PD assessed efficacy as a primary outcome measure. In a US/Canadian study, the Parkinson study group reported that there was a significant improvement from baseline in combined UPDRS-ADL/-Motor subscores, for rotigotine doses of 6 mg/24 h (- 5.09; $p = 0.001$) and 8 mg/24 h (- 5.30; $p < 0.001$), in comparison with placebo (- 0.29) [44]. This significant effect was apparent from week 4, and returned towards baseline immediately following medication withdrawal at week 11 (**Figure 3**) [44]. A further report of this study, which included 74 additional patients from Europe, Asia and South Africa, showed similar results, with statistical significance in the combined UPDRS-ADL/-Motor subscore for the 4 – 8 mg/24 h rotigotine groups [54]. In both reported data sets, there was a dose-response across the tested doses from 2 – 8 mg/24 h rotigotine, which reached a plateau between 6 and 8 mg/24 h [44,54]. On this basis, marketing authorization in the USA was provided for doses up to 6 mg/24 h, while in Europe maximal approved dose as monotherapy is 8 mg/24 h.

A second placebo-controlled Phase III study of rotigotine in early PD examined efficacy over a longer duration of 27 weeks [39,45]. In this study, rotigotine (≤ 6 mg/24 h) produced an approximate 5.3-point improvement in combined UPDRS-ADL/-Motor subscore versus placebo ($p < 0.0001$), with the UPDRS-Motor score having the greatest contribution to this improvement [39,45]. In addition, there was a significantly higher proportion of responders (≥ 20% decrease from baseline in UPDRS score) in the rotigotine group versus placebo (48% vs 19%; $p < 0.0001$) [45]. Rotigotine treatment also significantly improved clinical global impression versus placebo (57% vs 30%; $p < 0.001$), and was associated with a high quality of life [39]. A subgroup analysis of these results showed that the observed efficacy of rotigotine was independent of gender, age, disease severity and disease duration [55]. Furthermore, interim data from a long-term extension of this study indicate continued symptomatic improvement after an additional 85 weeks of open-label treatment with rotigotine [56]. In a third Phase III study, the efficacy of rotigotine in early PD was compared with that of ropinirole over a ~ 37-week period [46]. The proportion of responders (≥ 20% reduction in combined UPDRS-ADL/-Motor subscore) was significant for both rotigotine ≤ 8 mg/24 h (52%) and ropinirole ≤ 24 mg/day (68%), versus placebo (30%; $p < 0.0001$) [46]. Significant improvement was also observed in the absolute mean decrease from baseline in combined UPDRS-ADL/-Motor subscores for rotigotine (- 7.2), and ropinirole (- 11.0), versus placebo (- 2.2; $p < 0.0001$) [46]. Median doses of rotigotine and ropinirole were 8 mg/day and 14.1 mg/day, respectively. In this study, rotigotine did not show non-inferiority to ropinirole in responder rate. The authors postulated that rotigotine-treated patients might have been under-dosed compared with patients receiving ropinirole. The problem of dose equivalence when comparing the efficacy of different dopamine agonists is crucial, and remains unsolved. Additionally, the maintenance phase for the ropinirole lasted for 3 weeks longer than for rotigotine. Therefore, a *post hoc* subgroup analysis was made to compare mean change from baseline in combined UPDRS-ADL/-Motor subscore between the subgroup that received ropinirole at doses ≤ 12 mg/day and the rotigotine-treated group, adjusting for the aforementioned difference in the maintenance phase length [46]. A non-significant difference < 1 point ($p = 0.5$) was found, which is obviously not sufficient to claim non-inferiority, but further indicates that the failure to show non-inferiority may be related to a dosage problem rather than to a difference in the agonists' efficacy.

Together, these Phase III study results support the efficacy of rotigotine monotherapy versus placebo in the treatment of early PD.

7.1.2 Adjunct therapy to levodopa in advanced Parkinson's disease – symptom control

Symptom control was examined as a secondary endpoint in two Phase II and two Phase III studies of rotigotine in advanced PD. The Phase II studies produced results in favour of rotigotine, although they were both short-term investigations involving relatively small patient numbers, with no placebo or comparator control [47,48]. In one study, rotigotine (≤ 16 mg/24 h) coadministration significantly reduced the median levodopa dose required from 1400 mg/day to 400 mg/day ($p = 0.018$), with no change in symptom control observed over a mean 11-day treatment period (UPDRS-Motor score) [47]. In the second study, rotigotine (≤ 24 mg/24 h) reduced UPDRS-Total score over a 12-week period [40,48].

In the controlled Phase III studies, rotigotine generated significant improvements in symptom control versus placebo [49,50]. In the PREFER Study, the rotigotine 8 and 12 mg/24 h patient groups showed significant improvements over placebo of 2.6 and 2.7 points in UPDRS-ADL score, and 3.4 and 5.3 points in UPDRS-Motor score, respectively [49]. Similar improvements in UPDRS-ADL and -Motor score in the ON condition ($p < 0.0001$ vs placebo) were observed in the CLEOPATRA-PD Study, with rotigotine doses up to 16 mg/24 h [50]. Quality of life was also improved with rotigotine treatment in this study, as measured by the PDQ-39 total score ($p = 0.003$ vs placebo) [50]. This overall improvement in quality of life was driven by the PDQ-39 subscores of mobility, ADL, and emotional well-being [50]. These efficacy results were

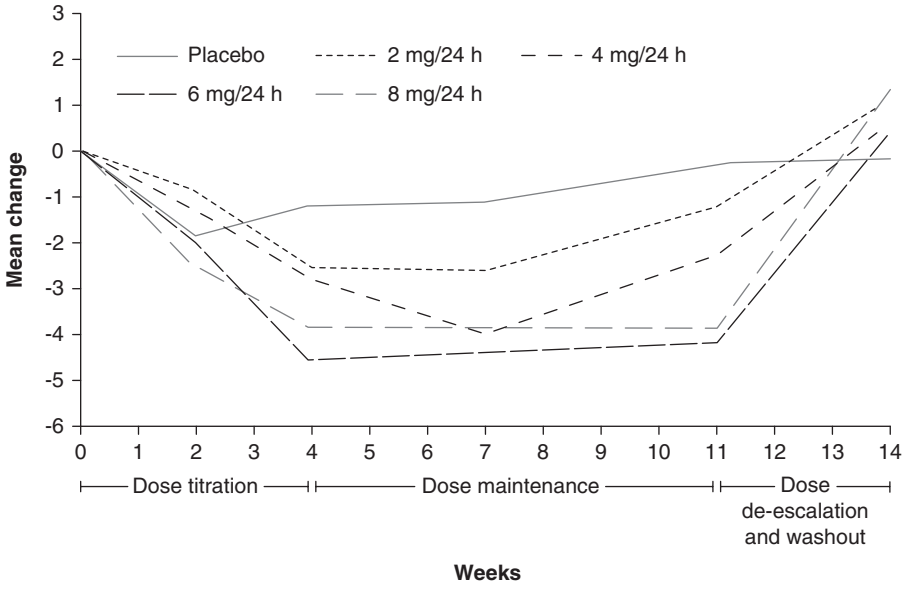

Figure 3. Mean change from baseline in UPDRS-ADL/-Motor subscores in early Parkinson's disease for rotigotine treatment groups [43].
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similar to those observed with the comparator agent, pramipexole [50]. A non-significant reduction in levodopa dose was also found, thus not reproducing previous Phase II results [53]. It should be mentioned that all these outcomes were secondary. Primary outcomes for this study are discussed in the following section.

7.1.3 *Control of motor complications*

Phase II data indicate that rotigotine treatment can produce a decrease in OFF time in patients with advanced PD. Babic *et al.* reported a 2 – 3-h reduction in mean daily OFF time, accompanied by an increase of approximately 2 h/day in mean ON time without dyskinesias [48]. In addition, the number of OFF periods decreased by 1.25 periods/day [48]. In the study by Verhagen Metman *et al.*, there was a significant decrease in OFF time of 37% ($p = 0.028$), alongside a non-significant increase in ON time without dyskinesia (62%) [47]. As described earlier, this latter result was in a patient population that had received significant levodopa dose back-titration [47]. However, both these studies were small in scale and had no placebo controls. A larger-scale, placebo-controlled Phase II study of rotigotine revealed a decrease in OFF time of 1.72 h/day and 2.44 h/day for 8 mg/24 h and 12 mg/24 h doses, respectively [51]. Although this magnitude of effect was comparable to that achieved by other dopamine agonists, there was a very strong placebo effect, and the rotigotine results did not reach statistical significance [51].

By contrast, two large-scale Phase III studies found that, over 6 months, rotigotine produced significant reductions in daily OFF time, as assessed by patients' 24-h home diaries [49,50]. In the PREFER Study, rotigotine produced significant adjusted mean decreases in OFF time versus placebo, with corresponding significant increases in ON time without troublesome dyskinesia, and no change observed in ON time with troublesome dyskinesias (**Figure 4**) [49]. In addition, the responder rate (≥ 30% reduction in OFF time) was higher with rotigotine treatment (55 – 57%), compared with placebo (35%) [49]. The CLEOPATRA-PD Study had similar findings and included oral pramipexole as an active comparator (**Figure 4**) [50]. Responder rates (≥ 30% reduction in OFF time) were 60, 67 and 35% for the rotigotine, pramipexole and placebo groups, respectively [50]. Therefore, the first comparative indications available for rotigotine for the treatment of motor fluctuations in PD, indicate significant efficacy and non-inferiority to pramipexole [50]. Mean rotigotine and pramipexole doses were 12.9 ± 3.5 mg/day and 3.1 ± 1.2 mg/day respectively.

In addition to benefiting the ratio of ON:OFF time, the steady delivery of the CDS method might be expected to target OFF problems at night, producing improvements in sleep and early morning motor function. Results from a Phase II study in advanced PD indicated that there was no change in sleep duration reported with rotigotine treatment (in comparison with baseline), although patient status after waking was noted to have shifted from OFF to ON without dyskinesia [48]. The Phase III PREFER Study found that the proportion of patients experiencing ON time without dyskinesia after waking more than doubled with rotigotine treatment, versus placebo [49]. A shift in waking status was also seen in the CLEOPATRA-PD Study:

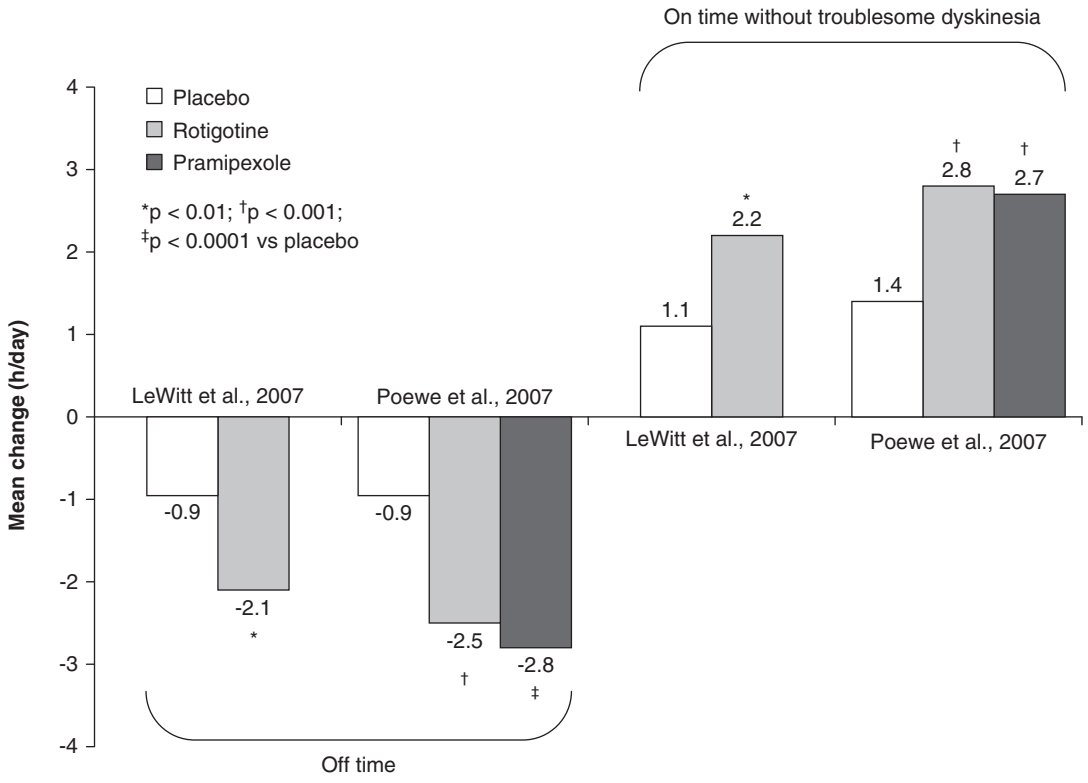

Figure 4. Change from baseline in daily time spent 'OFF' and 'ON without troublesome dyskinesia' in patients with advanced Parkinson's disease, receiving treatment with placebo, rotigotine or pramipexole [48,49].

OFF-time decreased with respect to baseline by 0.9 h/day in the placebo group, 2.8 and 2.5 h/day in the pramipexole and rotigotine groups, respectively (both $p < 0.0001$ vs placebo) [50]. No major between-group differences were found in ON-time with or without dyskinesias. A significant improvement in the PD sleep scale score (measuring sleep problems and nocturnal disability) of 7.7 and 7.1 points in pramipexole and rotigotine groups compared with placebo ($p < 0.0001$ and $p < 0.001$ respectively) was observed [50] Furthermore, in an open-label study ($n = 54$), patients showed significant improvements in nocturnal and motor status upon awakening and experienced significantly fewer episodes of nocturia after 4 weeks of rotigotine treatment [57].

7.1.4 *Prevention of motor complications*

Early pulsatile dopaminergic stimulation of neurons via levodopa treatment has been associated with the development of motor complications. Thus, it has been suggested that the avoidance of this initial pulsatile stimulation may contribute to the prevention of motor complications later in the disease course [43,58]. In addition, clinical trials have revealed that early treatment with dopamine agonists produces fewer motor complications than levodopa in the long term [59-61].

Therefore, CDS delivery would appear to be a potentially useful strategy for use in the prevention of motor complications with early therapy. However, data for rotigotine are not yet available in this area.

7.1.5 *Disease progression*

The long-term effects of early treatment initiation with rotigotine is now being investigated in a 3-year open-label extension of a 6-month double-blind, placebo-controlled study of rotigotine in early PD [39,45,62]. Interim analyses from this study extension indicate that patients who received rotigotine throughout both study phases have a persistent advantage in symptom control over patients who received placebo for the first 6-month phase of the study [62]. Further analysis of these study results, when fully published, is required. At present, there is no definite evidence that rotigotine has any impact on disease progression. This applies to all anti-Parkinsonian medications marketed at present.

7.1.6 *Treatment switch*

An open-label study by Lewitt *et al.* of 116 PD patients investigated the overnight switch from oral therapy with low/moderate doses of oral dopamine agonists (ropinirole ≤9 mg/day, cabergoline ≤3 mg/day or

pramipexole ≤ 2 mg/day) to corresponding doses of rotigotine (dose equivalence ratios of 1:1, 1:2.5 and 1:4, for ropinirole, cabergoline and pramipexole to rotigotine, respectively) [63]. Overnight switch from one dopamine agonist to another may avoid hypodopaminergic-related increased parkinsonism, and has been shown to be at least as safe as slow titration [64-67] or even safer [65]. The study by Lewitt *et al.*, found that switching to rotigotine was well tolerated, provided control of PD symptoms, and over 80% of patients required no dose adjustment after starting rotigotine at the preselected dose [63].

7.1.7 *Other indications*

Although outside the scope of this review, rotigotine is also being developed for use in RLS. Phase II data indicate that the rotigotine transdermal patch can improve International RLS Study Group Rating Scale (IRLS), clinical global impression and RLS-6 severity scores [19,20].

7.2 Safety and tolerability

7.2.1 *General safety and tolerability*

The rotigotine safety and tolerability profile has been examined for treatment periods of up to ~ 8 months in double-blind studies [39,44-46,50,51]. Interim data from a 3-year open-label extension study of rotigotine in early PD are not reported to highlight any additional concerns [45,56].

Clinical studies in early and advanced PD found rotigotine to be generally safe and well tolerated, with most adverse events (AEs) being mild or moderate in severity, and occurring transiently. Pooled data from placebo-controlled studies (1083 rotigotine patients), found that 73.0% of rotigotine patients reported at least one AE, in comparison with 56.3% of placebo patients [21]. In this pooled population, the most common AEs, reported by ≥ 10% of patients, were nausea, dizziness and somnolence (effects consistent with dopaminergic stimulation; see below), and application site reactions [21]. In a small-scale dose-escalation study by Babic *et al.*, rotigotine doses up to 24 mg/24 h were found to be well tolerated [40,48], with slow and fast titration regimens (2 mg/24 h vs 4 mg/24 h increments per week) producing comparable AE profiles [40].

In one study of early PD, serious adverse events (SAEs) were reported in 4% of rotigotine-treated patients and 2% of placebo-treated patients [44]. These SAEs included sudden onset of sleep while driving, brief loss of consciousness while driving, and unconfirmed tachycardia [44]. In a second study in early PD, SAEs were reported by 10% of rotigotine patients versus 8% of placebo patients [46]. In advanced PD, SAEs occurred at a comparable level to placebo (9 vs 9%), with SAEs in rotigotine patients including nausea, dyskinesia, syncope, tachycardia, atrial fibrillation and application site reactions [50]. A recent study in patients with early PD investigated the use of rotigotine in patients undergoing surgery with general anaesthesia, and raised no additional safety issues [68].

In early PD, withdrawal rates were 9 – 29% for rotigotine-treated patients, compared with 15 – 28% for placebo patients [39,44-46]. In advanced PD, 11 – 27% of patients discontinued treatment with rotigotine, with withdrawal levels of 13 – 26% in placebo-treated patients [49-51]. The most common reason for withdrawal was AEs [44-46,49-51], and the overall rotigotine withdrawal rate was comparable to that of ropinirole (23%) in early PD, and pramipexole (15%) in advanced PD, in the comparator studies [46,50]. In both comparator studies, the AE most commonly leading to withdrawal in the rotigotine group was application site reactions [46,50]. Other AEs leading to withdrawal were similar between comparator groups, with the exception of hallucination/confusion and symptomatic orthostatic hypotension, which led to withdrawal in more pramipexole-treated patients than rotigotine-treated patients (see section 7.2.3) [50].

For treatment periods of up to 6 months, the compliance rate for rotigotine treatment was > 95% in both early and advanced PD [44,45,49,50], with a high level of compliance also reported after long-term treatment in early PD (85-week, open-label extension) [56]. With relevance to compliance, studies have also reported that patients prefer the transdermal patch over oral medication [56,69]. In one study, 82% of patients agreed to use a skin patch over oral medication; the reasons driving this preference included once-daily administration (85%) and not having to remember to take tablets during the day (87%) [69]. Overall, 95% of patients were satisfied or very satisfied with the rotigotine patch (vs 41% satisfaction with oral medication). The most common disadvantage cited was that the patch 'did not stay on for the entire day' (56%) [69].

7.2.2 *Application site reactions*

Overall, application site reactions were cited as the most common AEs in rotigotine clinical studies. As many as half of rotigotine patients had application site reactions (including erythema, pruritus and dermatitis), compared with 11 – 21% of patients receiving placebo treatment [39,44-46,49]. However, the majority of these events were rated as mild to moderate [44,46,51], and appeared to be dose related [44]. In total, 1 – 8% of rotigotine patients withdrew because of application site events [39,44-46,49] and, in the PREFER Study, most reactions spontaneously resolved without necessitating a change in dose [49]. The rotigotine prescribing information recommends that the patch application site should be switched on a daily basis [21]. If additional treatment is needed, it can be recommended as for other transdermal systems, i.e., moisturising, gentle skin care, and application of topical corticosteroids at the previous patch sites [70]. The manufacturer recommends discontinuing rotigotine if generalized skin reactions are observed and, considering the risk:benefit ratio, if a patient reports a persistent application site reaction (of more than a few days), an increase in severity, or a skin reaction spreading outside

the application site [21]. The rate at which the patch detached from the patients' skin has not been reported.

7.2.3 Dopaminergic adverse events

As would be expected with a dopamine agonist, the most commonly reported AEs with rotigotine treatment (aside from application site reactions) were dopaminergic-specific AEs including nausea, vomiting, somnolence, and dizziness [44-46,49-51]. The occurrence of these AEs seemed to be dose-related in some cases, for example nausea and somnolence [44] and were most frequent during dose titration [44,49]. The incidence of dopaminergic AEs in four double-blind, placebo-controlled, 6 – 8-month rotigotine studies is shown in **Table 2**. In general, hallucinations, peripheral oedema and orthostatic hypotension were dopaminergic AEs that were observed at relatively low rates in several studies [44,45,50], although raised rates of hallucinations and peripheral oedema were observed with rotigotine in one study in advanced PD at both the 8 mg/24 h and 12 mg/24 h target doses [49]. In the comparator study in advanced PD, more pramipexole-treated patients than rotigotine-treated patients withdrew owing to orthostatic hypotension (5 patients vs 1 patient) and hallucinations/confusion (4 patients vs 0 patients) [50].

In the comparator study in early PD, lower frequencies of nausea, dizziness and somnolence were observed with rotigotine treatment compared with ropinirole treatment [46]. Excessive sleepiness was reported by 8% of rotigotine patients, compared with 14% of ropinirole patients (6% of placebo patients), and sleep attacks occurred in 3% of rotigotine patients and 2% of ropinirole patients (no placebo patients) [46]. Somnolence was consistently reported as a common AE in rotigotine studies, reaching an incidence of 33% (vs 20% placebo) in one study on early PD [45]. However, measurements on the Epworth Sleepiness Scale (ESS) in two different trials [39,50] failed to reveal significant differences between patients treated with rotigotine or placebo, although these trials were probably not sufficiently powered to find differences in such an outcome. None of these studies investigated sudden onset of sleep episodes. It is unclear whether the ESS is predictive of 'sleep attacks', although the occurrence of sudden sleep episodes has been reported to be predicted by an ESS score ≥ 10 [71,72]. Sudden onset of sleep was reported as an SAE in one study [44].

'Impulse control disorders' and 'dopamine dysregulation syndromes' that have been recently reported with various dopamine agents [73,74] have not been specifically studied in clinical trials with rotigotine, and therefore further data are needed to draw conclusions.

7.2.4 Other safety issues

As a non-ergoline derivative, rotigotine is not expected to induce fibrosis concerns that have been reported with other dopamine agonists including bromocriptine, pergolide and cabergoline [75-77], but long-term, post-marketing surveillance is required to confirm this expectation.

7.3 Pharmacoeconomic aspects

There is no cost-effectivity or cost-efficacy analysis available for rotigotine. Pham and colleagues have recently noted that the monthly cost of 4 mg/day of rotigotine (i.e., the lowest effective dose) would be US$277.2 [78]. On the other hand, the monthly cost of pramipexole 1.5 mg TID would be US$216.64, while the cost of ropinirole 2 mg TID is US$140.40. The costs herein reported have to be evaluated against the risk/benefit of each drug before any further consideration.

8. Expert opinion

The rotigotine transdermal patch offers an innovative approach for the treatment of PD and is a welcome addition to drug delivery in this field. From available study data, it is clear that the rotigotine patch demonstrates clinical efficacy in PD, as would be expected from any D_2 dopamine agonist. Its maximum recommended dose levels may require more precise definition – particularly as they differ between early (up to 8 mg/24 h) and advanced PD (up to 16 mg/24 h) – although physical limitations related to the surface of the patch might be a practical limiting factor. The tolerability of the rotigotine patch appears to be well within the range of what is known and expected from other non-ergot dopamine agonists (except for application-site reactions). The rotigotine transdermal administration may, in theory, deliver more continuous dopaminergic stimulation than traditional immediate-release oral agents, and this could translate into a reduced emergence of motor complications, according to the hypothesis of 'continuous dopamine stimulation'. However, no long-term, levodopa-controlled, comparative prospective trial has been conducted to test this possibility with rotigotine. This is unfortunate, especially because such trials are available with other orally acting agonists such as ropinirole and pramipexole. The continuous transdermal administration method may also have further potential advantages versus orally active agonists. For example, tolerance to peripheral AEs such as gastrointestinal events might theoretically develop faster (i.e., more rapid desensitization) with a constant drug plasma level. Such a hypothesis should be better explored in comparative trials. Furthermore, it is common knowledge that some patients typically experience somnolence at 1 – 2 h following ingestion of orally administered dopamine agonists (i.e., at C_{max}). These patients might be expected to have fewer problems with a drug that exhibited more even plasma levels with no peaks, although somnolence has been reported with rotigotine treatment in published clinical trials. This should also be better explored in post-marketing surveillance. The possibility that constant stimulation could lead to partial desensitization of dopamine

Table 2. Incidence of dopaminergic adverse events in three 6-month double-blind, placebo-controlled studies of rotigotine in early and advanced Parkinson's disease [44,45,48,49].

	Frequency of adverse events (%)									
	Giladi *et al.*, 2007a (early PD)*			Watts *et al.*, 2007 (early PD)‡		LeWitt *et al.*, 2007a (advanced PD)§		Poewe *et al.*, 2007 (advanced PD)*		
	Placebo (n = 118)	Rotigotine ≤ 8 mg/24 h (n = 215)	Ropinirole ≤ 24 mg/day (n = 228)	Placebo (n = 95)	Rotigotine ≤ 6 mg/24 h (n = 181)	Placebo (n = 120)	Rotigotine ≤ 12 mg/24 h (n = 111)	Placebo (n = 101)	Rotigotine ≤ 16 mg/24 h (n = 204)	Pramipexole ≤ 4.5 mg/day (n = 201)
Constipation	4	7	9	4	6	6	5	–	–	–
Diarrhoea	4	4	6	2	6	–	–	–	–	–
Dizziness	10	14	17	13	19	15	15	4	6	10
Dyskinesia	–	–	–	–	–	7	17	3	12	15
Hallucinations	–	–	–	1	0	3	14	1	5	7
Nausea	16	29	36	17	41	20	24	11	17	13
Vomiting	3	12	11	1	9			–	–	–
Orthostatic hypotension	–	–	–	4	2	7	2	5	3	5
Peripheral oedema	–	–	–	3	3	< 1	14	–	–	–
Somnolence	20	23	28	20	33	28	32	8	12	12

*Reported AEs at a frequency of ≥ 5% in any group; ‡Reported AEs at a frequency of > 5% in the rotigotine group; §Reported 'most common' AEs; Combined category, 'nausea and vomiting'.

receptors – a disadvantage in terms of efficacy – should also be considered. The fact that rotigotine did not show non-inferiority in a trial versus ropinirole raises this question. However, the finding that rotigotine was non-inferior to pramipexole in another trial suggests that methodological issues (such as dose equivalence problems), rather than a true desensitization phenomenon or real biological inferior potency, are more likely to be involved. All these potential effects require further explanation and support from clinical data. Crystallization of rotigotine within the patch has been show to compromise bioavailability and thus efficacy. Refrigerated storage of the patches can solve this issue but introduces practical inconveniences for product distribution and storage. The once-daily transdermal patch formulation may favour compliance, by providing a convenient means of administration. Post-marketing surveillance should provide further support for this advantage in the future. Following the recent development of controlled-release formulations of dopamine agonists such as ropinirole CR and pramipexole ER, it remains to be seen how the potential practical benefits of a once-daily patch application compare with those of a once-daily tablet. On the contrary, the benefit for patients with swallowing disorders seems undisputable.

Declaration of interest

Rascol has acted as a consultant for most of the drug companies active in the field of Parkinson's disease, including GSK, Novartis and UCB.

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