Rotigotine for the Treatment of Advanced Parkinson's Disease

Santiago Perez Lloret[1,2] and Olivier Rascol[1]

1. Department of Clinical Pharmacology and Neurosciences, Hospital and University Paul Sabatier of Toulouse, and INSERM CIC9023 and UMR 825, Toulouse; 2. Clinical Pharmacology Centre, Raul Carrea Institute for Neurological Research, Buenos Aires

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Abstract

Background: Rotigotine, a non-ergot dopamine agonist, has been developed as a novel transdermal formulation. The rotigotine transdermal patch is approved by the regulatory authorities for use in all stages of Parkinson's disease (PD) in Europe and for early-stage PD in the US. For patients with advanced-stage PD and motor fluctuations, approved doses range from 4mg/24 hours to 16mg/24 hours. The rotigotine patch offers a certain number of potential advantages, including faster onset as intestinal absorption is not needed, continuous drug delivery and ease of use via application of a once-daily adhesive patch. An interesting element of this profile is continuous drug delivery, which may avoid the pulsatile dopaminergic stimulation that has been postulated to be related to the development of motor complications. **Objective:** The aim of this article is to review the pharmacokinetics, pharmacodynamics and clinical efficacy and tolerability of the rotigotine transdermal patch. **Methods:** Source material was identified using a PubMed search for the term 'rotigotine' in articles published up to October 2009 and a review of published congress abstracts. The review focused primarily on publications related to the rotigotine indication for advanced PD. **Results and conclusions:** The rotigotine transdermal patch demonstrates clinical efficacy and a tolerability profile that appears to be well within the range of that observed with other non-ergot dopamine agonists, except for local skin reactions, which are common with the rotigotine patch. The once-daily patch formulation may encourage compliance; however, as is the case for other theoretical advantages of continuous drug delivery, such as reduced emergence of motor complications and improved tolerance of peripheral adverse events, this requires further detailed study.

Keywords

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

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Correspondence: Olivier Rascol, Department of Clinical Pharmacology, Faculty of Medicine, 37 Allées Jules Guesde, 31000 Toulouse, France. E: rascol@cict.fr

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Parkinson's disease (PD) is a progressive neurodegenerative condition[1] affecting over 1 million people in Europe[2] and North America.[3] A systematic review of 25 incidence studies found that in eight studies, the mean age of symptom onset was 60–65 years, and >65 years in five studies.[4] Unmet needs in PD therapy include 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 five years of therapy.[5,6] 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/or many other antiparkinsonian drugs.[7] 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 so-called 'continuous delivery system' (CDS).[8] In addition, multiple doses per day of orally active drugs can cause low compliance. According to one study, over 50% of PD patients miss at least one dose of medication per week, and approximately 20% of patients miss three or more doses per week.[9] Finally, dysphagia is frequent in PD[10] and can complicate oral delivery of drugs. This problem may be tackled by administering drugs by alternative routes, such as transdermally.

Transdermal administration of rotigotine may deal with these problems. First, such a continuous drug delivery has the potential to generate constant drug plasma levels.[11] Sustained administration of rotigotine has been shown to produce constant receptor stimulation,[12] which may help reduce or delay the occurrence of motor complications in PD, as shown in animal models.[13,14] Second, a long-acting CDS would potentially offer a simpler dosing system, promoting patient compliance and resulting in more consistent symptomatic effects. Finally, transdermal drug administration may be ideal for treatment of patients with dysphagia or severely retarded gastric emptying.

Rotigotine is a novel non-ergot dopamine agonist that also has 5-HT_{1A} agonistic and α_2-adrenergic antagonistic properties.[15,16] Neupro® (transdermal rotigotine patch, UCB Pharma GmbH) is the first transdermal patch to be approved by the regulatory authorities for use in all stages of PD in Europe and for early-stage PD in the US. For patients with advanced-stage PD and motor fluctuations, approved doses range from 4mg/24 hours to 16mg/24 hours.[17] This review will

focus primarily on rotigotine for advanced PD; for data about its effect in early PD, please see references 18 and 19.

Pharmacodynamics of Rotigotine

Rotigotine has agonistic activity at all dopamine receptor subtypes (D_1–D_5), but demonstrates its highest affinity for the D_3 receptor.[20] *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[20] – a profile consistent with that seen in other, earlier investigations.[15] A comparison of the affinity of rotigotine for dopamine receptors with those of other non-ergot agonists is shown in *Table 1*. Rotigotine has a similar affinity ratio to dopamine itself, with a preference for the $D_3/D_2/D_1$ receptors – the three major dopamine receptor subtypes expressed in the striatum.[21] Compared with pramipexole or ropinirole, rotigotine shows a higher affinity and similar selectivity for D_2-like dopamine receptor subtypes.[20,22,23] In addition, rotigotine acts as an antagonist at the α_2-adrenergic receptor and as an agonist at the $5HT_{1A}$ receptor.[15,16] *In vitro* functional assays have also demonstrated its inhibition of dopamine uptake and prolactin secretion.[15]

A slow-release form of rotigotine generated constant extracellular drug levels in the brains of freely moving rats following subcutaneous administration.[12] These levels were maintained for at least 48 hours and were accompanied by a concomitant and maintained reduction in extracellular dopamine to about 20% of vehicle control levels.[12] As dopamine synthesis is controlled by pre-synaptic receptors, this observation supports rotigotine's potential to induce continuous stimulation of dopamine receptors.[12]

Rotigotine has demonstrated benefits in several animal models of PD. In 6-hydroxy dopamine (6-OHDA)-lesioned rats, subcutaneous rotigotine induced dose-dependent contralateral turning behaviour.[15] Further to this, in a study of hemi-parkinsonian (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]-induced) monkeys, intramuscular rotigotine also induced contralateral turning behaviour, as well as exploratory activity and contralateral limb usage.[15] In the MPTP-lesioned common marmoset, subcutaneous rotigotine produced a dose-dependent increase in well co-ordinated locomotor activity, with a concomitant reduction in disability scores.[24] This was observed at even the lowest dose of rotigotine (0.019mg/kg).[24]

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.[25] Discontinuous delivery of rotigotine and levodopa produced increased sensitisation of locomotor activity to approximately the same extent, whereas continuous delivery of rotigotine did not produce this sensitisation.[25] 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.[19]

Recent data indicate that rotigotine may also have neuroprotective effects,[26–29] but these results have not been further explored in humans.

Pharmacokinetics of Rotigotine

Rotigotine pharmacokinetics were dose-proportional.[17] After administration of a rotigotine patch (2mg/24 hours) to eight healthy volunteers, a median maximum concentration (C_{max}) of 0.215ng/ml was observed at 16 hours after administration (time to maximum plasma concentration [t_{max}]), with an area under the plasma concentration–time curve from time zero to the last time-point (AUC_{0-tz}) value of 3.94ng.hr/ml.[30] Following patch removal at 24 hours, the rotigotine plasma concentration decreased with a median terminal elimination half-life of 6.82 hours.[30] In PD patients, steady-state pharmacokinetic studies showed a mean (± standard deviation [SD]) plasma concentration of rotigotine of ~0.9ng/ml after daily applications of an 8mg/24 hours patch.[31] Six different body sites were used for patch application.[31] In subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Rotigotine was not investigated in patients with severe hepatic impairment.[17]

Table 1: Receptor Affinity Profiles of Rotigotine, Pramipexole and Ropinirole

Ligand	hD1	hD2L	hD3
Pramipexole[22]	>10,000	1,698	10.5
Ropinerole[22]	>10,000	933	37.2
Rotigotine[20]	83.2	13.5	0.71

K_i values are shown (unit of measurement: nM). h = human.
For further information, see references 20 and 22.

Approximately 45% of the active drug substance within the patch is released to the skin in 24 hours.[17,32] Rotigotine's volume of distribution in humans is 84l/kg. Due to the transdermal administration route, food and/or gastrointestinal conditions are not expected to influence its pharmacokinetics.[17] The majority of the rotigotine dose is excreted in the urine (71%), with approximately 23% excreted in the faeces.[17]

The development of crystals in rotigotine patches, resulting from the presence of another polymorphic form of the drug substance, was recently noted.[19,33] In theory, occurence of rotigotine crystals may reduce rotigotine's bioavailability, and therefore refrigerated storage of the patches was introduced, substantially reducing the formation of crystals and addressing the problem. Nonetheless, because of this issue, marketing is suspended in the US at present.

Drug–Drug Interactions

Rotigotine showed no pharmacokinetic drug–drug interactions with omeprazole,[17] domperidone[34] or levodopa/carbidopa.[35] However, as with other dopamine agonists, when given concomitantly rotigotine may potentiate the adverse reactions of levodopa, including the exacerbation of pre-existing dyskinesia.

Clinical Studies of Rotigotine

Currently published clinical studies of rotigotine in advanced PD include two large-scale phase III studies and three phase II trials (see *Table 2*). Overall, these studies indicated that rotigotine is effective for the treatment of levodopa-related motor complications as well as for motor symptom control in advanced PD.

Treatment of Motor Complications

Phase II data indicate that rotigotine treatment can produce a decrease in OFF time in patients with advanced PD. Early uncontrolled studies showed reductions in mean daily OFF time and increases in mean ON time without dyskinesias.[19,36,37] A larger-scale placebo-controlled phase II study of rotigotine revealed a decrease in OFF time of 1.72 hours/day and 2.44 hours/day for the 8mg/24 hours and 12mg/24 hours doses, respectively.[38] Although this magnitude of

Table 2: Clinical Development Programme for Rotigotine

Phase	Study	Design	Rotigotine Dose	Comparator	Duration	No. of Patients	Outcomes
II	Metman et al., 2001[36]	Double-blind, dose-escalation	Up to 16mg/24 hours	Uncontrolled	4 weeks	7	P: levodopa dose S: UPDRS motor score without levodopa; total daily ON/OFF time
II	Rektor et al., 2009[37]	Open-label, randomised, dose-escalation	Up to 24mg/24 hours	Uncontrolled	12 weeks	34	P: tolerability S: total daily ON/OFF time; UPDRS total score
II	Quinn et al., 2001[38]	Randomised, double-blind	4, 8 or 12mg/24 hours	Placebo	12 weeks	324	P: safety and dose–response
III	LeWitt et al., 2007[39] – PREFER Study	Double-blind, randomised	8 or 12mg/24 hours	Placebo	29 weeks	351	P: total daily OFF time; responder rate S: daily ON time; number of OFF periods; UPDRS; other
III	Poewe et al., 2007[40] – CLEOPATRA-PD	Double-blind, randomised	Up to 16 mg/24 hours	Placebo, pramipexole	24 weeks	506	P: total daily OFF time; responder rate S: daily ON time; number of OFF periods; UPDRS; other

P = primary outcome; S = secondary outcomes; UPDRS = Unified Parkinson Disease Rating Scale.

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.

By contrast, large-scale phase III studies found that over six months rotigotine produced significant reductions in daily OFF time, as assessed by patients' 24-hour home diaries (see *Figure 1*).[39,40] In the Prospective Randomized Evaluation of a new Formulation: Efficacy of Rotigotine (PREFER) study, rotigotine produced significant 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 (see *Figure 1*).[39] The Clinical Efficacy of Pramipexole and Transdermal Rotigotine in Advanced Parkinson's Disease (CLEOPATRA-PD) study had similar findings, and included oral pramipexole as an active comparator.[40] Responder rates (≥30% reduction in OFF time) were 60, 67 and 35% for the rotigotine (mean daily dose 12.95mg/24 hours), pramipexole (mean daily dose 3.1mg/day) and placebo groups, respectively, indicating significant efficacy and non-inferiority to pramipexole.[40]

The PREFER study found that the proportion of patients experiencing ON time without dyskinesia after waking more than doubled with rotigotine treatment versus placebo.[39] A shift in waking status was also seen in the CLEOPATRA-PD Study, in which OFF time decreased with respect to baseline by 0.9 hours/day in the placebo group and by 2.8 and 2.5 hours/day in the pramipexole and rotigotine groups, respectively (both p<0.0001 versus placebo).[40] No major between-group differences were found in ON time with or without dyskinesias.

Rotigotine has also been shown to be useful for control of motor symptoms in particular situations, such as in patients with dysphagia.[41,42] Rotigotine may represent a useful treatment option due to its favourable receptor profile and unique application form. In particular, it may be helpful during specific situations such as acute surgery.[42]

Treatment of Motor Symptoms

The initial small, uncontrolled phase II studies produced results in favour of rotigotine.[36,37] In one study, rotigotine (≤16mg/24 hours) co-administration significantly reduced the median levodopa dose required from 1,400mg/day to 400mg/day (p=0.018), with no change in symptom control observed over a mean 11-day treatment period (Unified Parkinson Disease Rating Scale [UPDRS] motor score).[36] In the second study, rotigotine (≤24mg/24 hours) reduced UPDRS total score over a 12-week period.[37] Larger phase III studies confirmed these results (see *Figure 2*).[39,40] In the PREFER study, the rotigotine 8mg/24 hours and 12mg/24 hours patient groups showed significant improvements over placebo of, respectively, 2.6 and 2.7 points in the UPDRS activities of daily living (ADL) score and 3.4 and 5.3 points in the UPDRS motor score (see *Figure 2*).[39] Similar improvements in UPDRS ADL and motor scores in the ON condition (p<0.0001 versus placebo) were observed in the CLEOPATRA-PD study with rotigotine doses up to 16mg/24 hours (see *Figure 2*).[40] Quality of life was also improved with rotigotine treatment in this study, as measured by the Parkinson's Disease Questionnaire (PDQ)-39 total score (p=0.003 versus placebo).[40] This overall improvement in quality of life was driven by the PDQ-39 subscores of mobility, ADL and emotional wellbeing. These efficacy results were similar to those observed with the comparator agent, pramipexole. A non-significant reduction in levodopa dose was also found, thus not fully reproducing previous phase II results.[36,44]

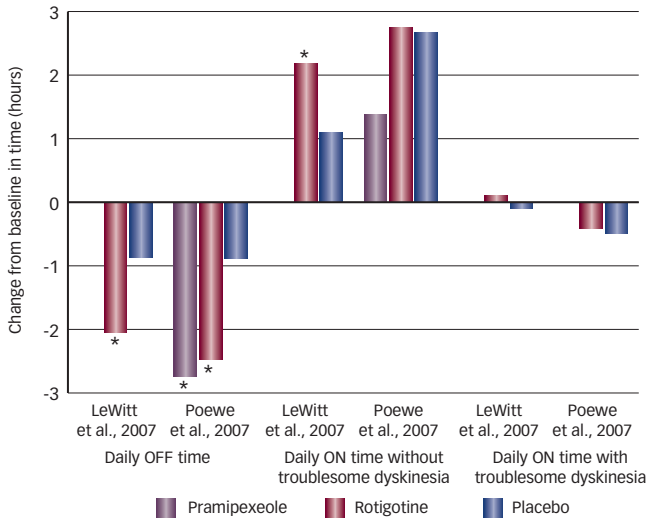
Effect on Sleep Quality and Nocturnal Motor Problems

A significant improvement in the PD sleep scale score (measuring sleep problems and nocturnal disability) of 7.7 and 7.1 points in the pramipexole and rotigotine groups, respectively, compared with placebo (p=0.0006 and p=0.0129, respectively) was observed.[40] 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 four weeks of rotigotine treatment.[19,45]

Safety and Tolerability of Rotigotine

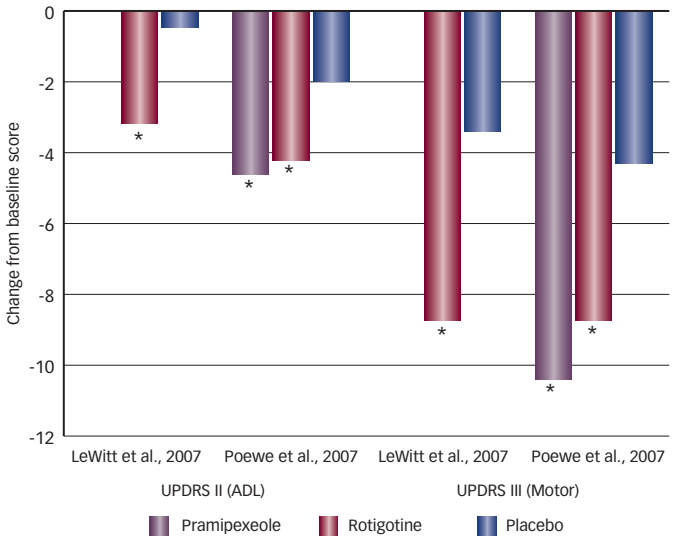
The safety and tolerability profile of rotigotine has been examined for treatment periods of up to approximately eight months in double-blind studies in early and advanced PD.[39,40,46–48] Interim data from a three-year open-label extension study of rotigotine in early PD are not reported to highlight any additional concerns.[19]

Figure 1: Change in Daily Time Spent in OFF or ON with or without Troublesome Dyskinesia



*Change is with respect to baseline in advanced Parkinson's disease patients on placebo, pramipexole or rotigotine as reported by Poewe et al., 2007[40] or LeWitt et al., 2007.[39] Only results obtained with the highest tolerable dose are shown. *p<0.01 versus placebo.*

Figure 2: Change in Unified Parkinson Disease Rating Scale Scores



*Change is with respect to baseline in advanced Parkinson's disease patients on placebo, pramipexole or rotigotine as reported by Poewe et al., 2007[40] or LeWitt et al., 2007.[39] Only results obtained with the highest tolerable dose are shown. *p<0.01 versus placebo. ADL = activities of daily living; UPDRS = Unified Parkinson Disease Rating Scale.*

Table 3: Frequency of Dopaminergic Adverse Events in Major Clinical Trials in Advanced Parkinson's Disease

	LeWitt et al., 2007[39]		Poewe et al., 2007[40]		
	Placebo (n=120)	Rotigotine ≤12mg/24 hours (n=111)	Placebo (n=101)	Rotigotine ≤16mg/24 hours (n=204)	Pramipexole ≤4.5mg/day (n=201)
Constipation	6	5	–	–	–
Dizziness	15	15	4	6	10
Dyskinesia	7	17	3	12	15
Hallucinations	3	14	1	5	7
Nausea	20	24	11	17	13
Vomiting			–	–	–
Orthostatic hypotension	7	2	5	3	5
Peripheral oedema	<1	14	–	–	–
Somnolence	28	32	8	12	12

All figures are percentages.

Clinical studies in early and advanced PD showed 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 in advanced PD found that the most common AEs, reported by ≥10% of patients, were nausea, dizziness, somnolence and application-site reactions.[17] The occurrence of dopamine-related AEs, which are shown in *Table 3*, appeared to be dose-related in some cases (e.g. nausea and somnolence), and were most frequent during dose titration. Increased rates of hallucinations and peripheral oedema were observed with rotigotine in one study in advanced PD at both the 8mg/24 hours and 12mg/24 hours target doses. In the comparator study, more pramipexole-treated patients than rotigotine-treated patients withdrew due to orthostatic hypotension (five versus one) and hallucinations/confusion (four versus none).[40] Recently, three cases of impulse-control disorders in patients on rotigotine patches have been reported; these were effectively treated by rotigotine reduction or discontinuation.[49] This alerts to the potential of rotigotine to cause these disorders, similar to other dopamine agonists. The frequency of serious AEs (SAEs) was comparable to that seen with placebo (8–9% for placebo, 9–10% for rotigotine).[40,46] SAEs in rotigotine patients included nausea, dyskinesia, syncope, tachycardia, atrial fibrillation and application-site reactions.[40]

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), in comparison with 4–21% of patients receiving placebo treatment.[39,40,46–48] However, the majority of these events were rated as mild to moderate, and appeared to be dose-related. In total, 1–8% of rotigotine patients withdrew due to application-site events, and in the PREFER study most reactions spontaneously resolved without necessitating a change of dose.[39,40,46–48] These types of reaction can be minimised by daily switching of the site of patch application.[50] If additional treatment is needed, moisturising, gentle skin care and application of topical corticosteroids at the previous patch sites are recommended. Rotigotine should be discontinued if generalised skin reactions are observed.

Withdrawal rates were as follows: 9–35% of patients discontinued treatment with rotigotine compared with 15–28% of those in the

placebo-treated group.[39,40,46–48] The most common reason for withdrawal was AEs, and the overall rotigotine withdrawal rate was comparable to that of pramipexole (15%).[40] In the latter study, the AE most commonly leading to withdrawal in the rotigotine group was application-site reactions.[40]

Rotigotine has been shown to be devoid of effect in cardiac repolarisation, even in supra-therapeutic doses.[51]

A recent small post-marketing study showed that in 12% of 150 patients on rotigotine, treatment was discontinued.[52] The reasons for withdrawal were worsening of the clinical condition, lack of effectiveness, drowsiness and dyskinesias.

Treatment Compliance

The compliance rate was high for rotigotine treatment, reaching 95% during the evaluation period (up to six months).[19] Patient preferences regarding rotigotine transdermal treatment were evaluated in a number of studies.[19] In general, patients stated that they preferred using the skin patch over oral medication because the possibility of once-daily administration reduced the burden of taking pill several times a day. On the other hand, 56% of patients reported that occasionally the patch did not stay on for the entire day.

Conclusion

The rotigotine transdermal patch has demonstrated clinical efficacy for the control of levodopa-related motor complications, while also showing antiparkinsonian effects. Tolerance of the rotigotine skin patch appears to be similar to other non-ergot dopamine agonists, with the exception of application-site reactions, which are unrelated to the drug's pharmacodynamics. Nonetheless, compared with the administration of agonist by immediate-release oral formulation, the rotigotine transdermal patch may provide more continuous dopaminergic stimulation. This in turn may help in reducing motor complications, according to the hypothesis of continuous dopamine stimulation. However, no data on the long-term prevention of dyskinesia are available to support this theory. The continuous transdermal administration method may also have further potential advantages over orally active agonists. First, a lower C_{max} level could reduce the incidence of drug plasma-level-dependent AEs, such as diurnal somnolence. Such a hypothesis should be better explored in comparative trials. Second, PD patients with swallowing disorders may obtain great benefits by avoiding the oral route. Finally, the once-daily transdermal patch formulation may favour compliance by providing a convenient means of administration. ■

Santiago Perez Lloret is Biomedical Research Co-ordinator at the Clinical Pharmacology Centre at the Institute for Neurological Research Raul Carrea (FLENI). He obtained his MD in 2004 and his PhD in 2009, and since then he has been working in the Department of Clinical Pharmacology at Toulouse University Hospital.

Olivier Rascol is a Professor of Clinical Pharmacology at Toulouse University Hospital. As a neuropharmacologist, his main fields of interest are Parkinson's disease and movement disorders, drug development for Parkinson's disease and functional neuroimaging. He has published nearly 300 articles in international scientific journals. Professor Rascol obtained his MD in neurology in Toulouse in 1985 and his PhD in neurosciences in Paris in 1992.

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