

Rotigotine transdermal system: a short review

Sabine Buntgen
Svenja Happe

Department of Clinical
Neurophysiology, Klinikum Bremen-
Ost/University of Göttingen,
Germany

Abstract: Rotigotine (Neupro®) is a new non-ergolinic dopamine agonist transdermal patch that can be applied once daily. To date, it is approved for the treatment of early Parkinson's disease as monotherapy and has been shown to be effective in the treatment of advanced-stage Parkinson's disease and restless legs syndrome in several clinical trials. This review gives an overview of physical, chemical, and pharmaceutical characteristics, pharmacokinetics, biotransformation and elimination, drug interactions, and adverse events of rotigotine. Further, the rationale for the treatment of Parkinson's disease and restless legs syndrome with rotigotine is discussed.

Keywords: rotigotine, transdermal patch, Parkinson's disease, restless legs syndrome

Physical, chemical and pharmaceutical characteristics

Rotigotine (Neupro®) belongs to the group of non-ergolinic dopamine agonists and shows agonistic activity on all dopamine (DA) receptors with a clear (about 20-fold) preference for the D3 over the D2 and (about 100-fold) over the D1 receptor (Jenner 2005). Antagonistic activity on alpha-2B-receptors and agonistic activity on 5HT1A receptors were also observed.

Its chemical name is (6S)-6-{propyl[2-(2-thienyl)ethyl] amino}-5,6,7,8-tetrahydro-1-naphthalenol (IUPAC nomenclature). The International Nonproprietary Name (INN) rotigotine for the active substance was approved by the World Health Organization (WHO) in 2000.

Pharmacokinetics

The earliest studies conducted with the aminotetralin derivate N-0437 led to the development of the (-)-enantiomer of N-0437 which became known as N-0923, and later as rotigotine (Jenner 2005).

In early trials, the aminotetralin derivate N-0437 proved to have only a short duration of effect on oral administration but a significantly prolonged effect after transdermal application (Loschmann et al 1989; Timmermann et al 1989). Nowadays, rotigotine is available only for transdermal drug delivery as a patch due to an extensive gastrointestinal metabolism (Swart and de Zeeuw 1992). It has been designed as a matrix-type transdermal system and consists of a backing film, a drug loaded matrix, and a protective liner (Pfeiffer 2005). The patch releases the active substance continuously over 24 hours following application to intact skin. Through transcellular, intercellular, follicular, and eccrine routes, lipophilic and hydrophilic penetration is achieved. For further pharmacokinetic details see Table 1.

The rotigotine patch is available in seven patch sizes, varying from a drug load of 1.125 mg up to 27.0 mg resulting in apparent doses of 0.5–12.0 mg per 24 hours (Schwarz Pharma 2005 17 October, pers comm). The surface area of the patch is directly proportional to the amount of active ingredient released from each patch per

Correspondence: Svenja Happe
Department of Clinical
Neurophysiology/University of
Göttingen, Züricher Str. 40, 28325
Bremen, Germany
Tel +49 241 408 2370
Fax +49 241 408 2375
Email svenja.happe@klinikum-bremen-
ost.de

Table 1 Single-dose pharmacokinetic profile of rotigotine (10 cm² transdermal patch applied for 24 hours) in healthy volunteers (values are medians)

C_{max}	0.215 ng mL ⁻¹
t_{max}	16 hours
AUC 0-tz	3.94 ng h ⁻¹ mL ⁻¹
t_{1/2}	6.82 hours

day; therefore the patch surface area varies from 2.5 cm² up to 40 cm² (Braun et al 2005b).

Biotransformation and elimination

Rotigotine is eliminated by extensive biotransformation such as N-dealkylation, sulfation, and glucuronidation. After transdermal application, the amount excreted in urine mainly consisted of conjugates of rotigotine. Less than 0.1% of the rotigotine dose absorbed was eliminated unchanged in the urine. After administering radiolabeled rotigotine intravenously, accumulated excretion of total radioactivity (0–261 hours) amounted to about 75% in the urine and about 25% in the feces (Cawello et al 2005).

A clinical trial including healthy subjects (creatinine clearance, CL_{Cr} >80 mL/min), subjects with moderate impairment of renal function (50 mL/min >CL_{Cr} ≥30 mL/min), severe impairment of renal function (CL_{Cr} <30 mL/min) and endstage renal impairment requiring dialysis (CL_{Cr} <15 mL/min) demonstrated that AUC, C_{max} and t_{1/2} for rotigotine in subjects with different stages of renal impairment and healthy subjects are similar. The data indicate that an adjustment of the dosing and titration scheme of rotigotine is not required based on impairment of renal function (Cawello et al 2005).

In case of an adverse drug reaction the short plasma elimination half-life of the drug leads to a rapid decrease in plasma drug levels once the patch is removed (Rascol 2005). According to Reynolds et al (2005) and Cawello et al (2005), plasma concentrations of rotigotine decreased with a median terminal elimination half-life (t_{1/2}) of 6.82 hours after patch removal at 24 hours.

Drug interactions

Although rotigotine has been developed for the treatment of Parkinson's disease, a clinical trial to investigate pharmacokinetic interactions between steady-state treatment with rotigotine transdermal patch and oral levodopa/carbidopa was, due to tolerability reasons, performed in

subjects who were being treated with levodopa/carbidopa for restless legs syndrome (RLS).

The open-label, parallel group design study included 24 patients with RLS. One subject dropped out due to adverse events; in the remaining 23 subjects, no effect of transdermal rotigotine 9 mg/day on the pharmacokinetics of levodopa/carbidopa 100 mg/25 mg twice daily was evident. Furthermore, the steady-state pharmacokinetics of rotigotine were not altered by co-medication with oral levodopa/carbidopa (Braun et al 2005a).

Based on these data, further clinical studies with rotigotine transdermal as adjunctive therapy to levodopa in patients with advanced-stage Parkinson's disease were performed (LeWitt et al 2005).

The drug–drug interaction potential related to cytochrome P450 (CYP)-dependent drug metabolism was investigated in vitro and in vivo, concluding that several CYP isoforms are capable of metabolizing rotigotine in the human liver. A selective inhibition of CYP isoforms does not extensively inhibit rotigotine metabolism in vitro. At therapeutic concentrations, rotigotine and its phase one metabolites are not considered to significantly inhibit or induce CYP enzymes. Co-medication with a non-specific CYP inhibitor does not alter pharmacokinetics of rotigotine in vivo in human subjects (Hansen 2005).

Adverse events

The most frequent (>20%) treatment-related adverse events (monotherapy with 10–40 cm² patches applied once daily) were application site reactions, nausea, and somnolence, all mild or moderate in severity (Reynolds et al 2005). The adverse events occurring in the two major studies with early Parkinson's disease patients are described in more detail below (see also Table 2).

Table 2 Most common adverse events in study SP 512, early-stage idiopathic Parkinson's disease (Watts et al 2004)

Adverse events	Placebo (N=95)	Rotigotine (N=181)
Application site reaction	11 (12%)	79 (44%)
Nausea	16 (17%)	75 (41%)
Somnolence	19 (20%)	60 (33%)
Dizziness	12 (13%)	34 (19%)
Headache	9 (9%)	29 (16%)
Vomiting	1 (1%)	16 (9%)
Insomnia	3 (3%)	17 (9%)
Dyspepsia	1 (1%)	12 (7%)
Diarrhea	2 (2%)	11 (6%)
Constipation	4 (4%)	11 (6%)
Tremor	4 (4%)	11 (6%)

A clinical trial with rotigotine transdermal as adjunctive therapy to levodopa in advanced-stage Parkinson's disease subjects who were inadequately controlled with levodopa included 260 subjects who completed the trial and who were randomized into 3 different groups. The placebo group consisted of 120 subjects, 118 subjects received rotigotine 40 cm² (18.0 mg total drug content), and 111 subjects received rotigotine 60 cm² (27.0 mg total drug content).

The duration of this trial was 33 weeks: a 4-week pre-treatment phase, a 5-week titration phase, and a 24-week maintenance phase. In the groups treated with rotigotine, application-site reactions were the most frequent adverse events, more often in the higher dosage group, 46% compared with 36% in the group treated with 40 cm², and the placebo group at 13%.

Somnolence was the second most frequent adverse event, 32% in both groups treated with rotigotine and 28% in the placebo group, followed by nausea, 22% in the rotigotine treatment group with 60 cm² and 28% in the 40 cm² treatment group, and the placebo group 18%. Other adverse events were vomiting, peripheral edema, falls, arthralgia, dizziness, dyskinesia, headache, insomnia, and hallucinations (LeWitt et al 2005). For a detailed listing of adverse events see Table 3.

A study including 285 RLS patients treated with rotigotine (dosages from 1.125 mg [2.5 cm²] up to 9.0 mg

[20 cm²]) and 55 RLS patients receiving placebo listed application-site reaction as the most frequent adverse event in the treatment group with 17.5% as opposed to the placebo group with an incident rate of 1.8%, followed by nausea 14.7% in the treatment group, 9.1% in the placebo group. Further adverse events with an incidence \geq 5% in the treatment group were influenza-like symptoms (8.4% in the treatment group, 9.1% in the placebo group), headache (7.4% in the treatment group, 7.3% in the placebo group), fatigue (7.0% in the treatment group, 9.1% in the placebo group), pruritus (5.3% in the treatment group, 1.8% in the placebo group), back pain (4.6% in the treatment group, 3.6% in the placebo group), and dizziness (4.2% in the treatment group, 7.3% in the placebo group). Withdrawal due to adverse events was 4.5% in the rotigotine group and 5.5% in the placebo group (Oertel et al 2005).

Rationale for treatment with rotigotine

Levodopa and dopamine agonists are primarily prescribed for Parkinson's disease and have been or are under investigation for the treatment of RLS (Stiasny et al 2000; Happe and Trenkwalder 2004; Thorpy 2005). Oral drug therapy is currently the accepted standard treatment, although the pulsatile stimulation of dopamine receptors has been recognized as an important mechanism in the generation of various complications, such as motor fluctuations and dyskinesias in patients with Parkinson's disease (Olanow and Obeso 2000). In comparison with levodopa, dopamine receptor agonists have a longer half-life, but with the possible exception of cabergoline and its half-life of approximately 65 hours, they do not provide continuous dopaminergic stimulation when administered orally at conventionally prescribed dosage frequencies (Pfeiffer 2005). In the past, non-oral options of drug delivery have been employed including intraduodenal levodopa, subcutaneous apomorphine and even intravenous infusions in order to provide a constant rate of drug delivery and therefore more constant, physiological dopamine receptor stimulation. In contrast to the deliveries mentioned above, transdermal drug delivery would be non-invasive and simple to use. Problems that had to be solved for this route of treatment were the enhancement of skin permeation to improve the effectiveness of transdermal drug delivery. Levodopa and many dopamine agonists are not sufficiently soluble to be administered transdermally.

Table 3 Most common treatment-emergent adverse events in advanced-stage Parkinson's disease (LeWitt 2005)

Adverse event	Placebo (N=120)	Rotigotine 18.0 mg daily (N=118)	Rotigotine 27.0 mg daily (N=111)
Application and instillation site reactions	16 (13%)	43 (36%)	51 (46%)
Application site erythema	4 (3%)	24 (20%)	21 (19%)
Application site pruritus	4 (3%)	15 (13%)	21 (19%)
Somnolence	33 (28%)	38 (32%)	36 (32%)
Nausea	22 (18%)	33 (28%)	24 (22%)
Dyskinesia	8 (7%)	16 (14%)	19 (17%)
Dizziness	18 (15%)	27 (23%)	17 (15%)
Fall	21 (18%)	14 (12%)	17 (15%)
Peripheral edema	1 (<1%)	11 (9%)	15 (14%)
Insomnia	7 (6%)	8 (7%)	15 (14%)
Vomiting	7 (6%)	12 (10%)	9 (8%)
Hallucination	3 (3%)	4 (3%)	11 (10%)
Arthralgia	8 (7%)	13 (11%)	10 (9%)
Headache	10 (8%)	12 (10%)	9 (8%)

To date, rotigotine transdermal has been approved for monotherapy of early Parkinson's disease only. It is an off-label medication for RLS and advanced Parkinson's disease.

Table 4 shows an overview of indication, administration, and dosing of rotigotine.

Rotigotine in Parkinson's disease

First described in 1817 by James Parkinson, this common disease with a prevalence ranging from 100 to 200/100 000 inhabitants shows a rise in incidence with advancing age. The underlying degenerative process is progressive despite the use of symptomatic drugs (Oertel and Quinn 1997). Resting tremor, rigidity of skeletal muscles, bradykinesia-akinesia, impairment of postural reflexes, gait disturbances, and autonomic symptoms present the clinical diagnostic features.

Currently available therapies consist of the oral administration of levodopa combined with peripheral dopa-decarboxylase (DDC) inhibitors and catecholamine-o-methyltransferase (COMT) inhibitors in order to prolong the half-life of levodopa. In addition, different dopamine agonists are used in clinical practice, which can be divided in two groups: non-ergolinic and ergolinic substances. Bromocriptine, pergolide, lisuride, and cabergoline are ergolinic dopamine agonists. Pramipexole and ropinirole are considered standard non-ergolinics. Only one (lisuride) of the above-mentioned drugs can be administered transdermally, though some can be administered intravenously or subcutaneously. However, this is not an option with many parkinsonian patients.

According to the above-mentioned concept that constant dopaminergic receptor stimulation should be favored instead of a pulsatile stimulation in order to minimize complications such as dyskinesias and unpredictable on-off motor fluctuations, a drug that can be administered continuously without any invasive methods such as transdermally should be considered a welcome alternative to the treatment options to date.

With the exception of lisuride, other previous attempts at using a transdermal delivery with dopamine agonists did not prove to be clinically effective, such as the naphthoxazine derivative naxagolide (+)-PHNO (Coleman et al 1989).

To date, two different clinical studies with early Parkinson's disease including a total of 242 and 277 patients have shown a positive treatment effect for rotigotine transdermal (The Parkinson Study Group 2003; Watts et al 2004).

Table 4 Indication, administration, and dosing of rotigotine patches

Indication

Idiopathic Parkinson's disease
Restless legs syndrome

Administration

Transdermal patch, applied once daily

Suggested dosage

Parkinson's disease

Monotherapy in early disease 10–40 cm² (total drug content: 4.5–18.0 mg), delivered apparent dose 2.0–8.0 mg per 24 hours

Adjunctive therapy in advanced disease 20–60 cm² (total drug content: 9.0–27.0 mg), delivered apparent dose 4.0–12 mg per 24 hours

Restless legs syndrome

2.5–20 cm² (total drug content: 1.125–9.0 mg), delivered apparent dose 0.5–4.0 mg per 24 hours

The Parkinson Study Group included 242 patients with early Parkinson's disease not receiving any other dopaminergic medication in a randomized, double-blind, placebo-controlled fashion. Selegiline, amantadine, or anticholinergic drugs were allowed, providing a stable dosage for 28 days before baseline and during the trial. Treatment options were patches containing 4.5, 9.0, 13.5, or 18.0 mg of rotigotine (with patch sizes from 10 cm² to 40 cm²) or placebo for 11 weeks. The doses delivered from these patches through the skin per day are 2, 4, 6, or 8 mg (apparent dose) (Schwarz Pharma 2005 17 October, pers comm). The change in the sum of the scores of the activities of daily living and motor components of the Unified Parkinson's Disease Rating Scale (UPDRS) from baseline to the end of treatment were evaluated. There was a significant dose-related improvement for the 13.5-mg and 18.8-mg groups compared with placebo. Adverse events like nausea, application site reactions, dizziness, insomnia, somnolence, vomiting, and fatigue occurred more often in subjects randomized to active treatment than placebo. Eight patients withdrew due to application-site reaction, two patients because of sudden onset of sleep or a brief loss of consciousness, and another two due to headache. Two serious adverse events were considered related to the study drug, one case of sudden onset of sleep while driving and one case of brief loss of consciousness while driving (The Parkinson Study Group 2003).

Another randomized, multicenter, double-blind, placebo-controlled trial included 277 patients with early Parkinson's disease and had a treatment duration of 27 weeks. With a ratio of 2:1, patients were randomized to receive either rotigotine or placebo. Those receiving rotigotine were

treated with a weekly increasing dose of 4.5 mg up to an optimal response or a maximum dose of 13.5 mg daily. Ninety percent of the patients with active treatment received 13.5 mg daily at week 27. Significant improvements could be observed in the UPDRS subtotal of parts 2 and 3 at the end of treatment. Adverse events compared with the placebo group consisted of application-site reaction (placebo 12%, rotigotine 44%), nausea (placebo 17%, rotigotine 41%), somnolence (placebo 20%, rotigotine 33%), dizziness (placebo 13%, rotigotine 19%), and headache (placebo 9%, rotigotine 16%). Further less frequent adverse events were vomiting, insomnia, dyspepsia, diarrhea, constipation, and tremor (Watts et al 2004).

An in-patient study included 10 subjects with advanced Parkinson's disease. Two administrative dropouts and one elimination due to recrudescence of hallucinations led to only 7 subjects whose data could be evaluated. The median daily UPDRS scores were unchanged. The reduction in off-time reached statistical significance. Adverse events were mild and consisted mainly of dopaminergic side effects and local skin reactions (Metman et al 2001).

Rotigotine in RLS

The clinical diagnostic criteria of RLS are uncomfortable or unpleasant sensations in the legs (sometimes in the arms) accompanied by an urge to move them. These symptoms begin or worsen during periods of rest or inactivity, are usually worse during the evening or at night-time or exclusively occur then, and are partially or totally relieved by movements (Allen et al 2003). The clinical criteria were established first by the International Restless Legs Syndrome Study Group in 1995 (Walters 1995) and modified in 2003 (Allen et al 2003).

Although the pathophysiology of RLS is not yet known, effective treatment primarily with dopaminergic drugs is established. In addition to levodopa and dopamine agonists, opioids, gabapentin and other anticonvulsants are helpful (Trenkwalder et al 2005).

Levodopa relieves the symptoms but carries the risk of inducing augmentation (Allen et al 2003; Happe and Trenkwalder 2004). Augmentation is defined as an earlier onset of symptoms during the day, an increase in severity of symptoms, and the involvement of other body parts (Allen et al 2003). Dopamine receptor agonists carry a lower likelihood of augmentation compared with levodopa and a good tolerability associated with a longer half-life (Happe and Trenkwalder 2004). To date, ropinirole is the only drug

approved in the US for the treatment of RLS. In some European countries, levodopa-benserazide is approved for the treatment of RLS. Pramipexole and ropinirole have been recently approved for the treatment of RLS in Europe.

A pilot study enrolling 68 patients with moderate to severe idiopathic RLS, of whom 63 were randomized, was conducted. The patients received either different patches loaded with 3 different doses of rotigotine (1.125 mg, 2.25 mg, and 4.5 mg), corresponding to apparent doses of 0.5–2.0 mg per 24 hours, or placebo. To determine efficacy, the total score of the International Restless Legs Syndrome Scale (IRLS), the RLS-6 scale, and the Clinical Global Impressions (CGI) were evaluated in addition to a sleep diary. The severity of RLS improved on the IRLS with all three dosages of rotigotine. The RLS-6 scales showed improvement of daytime symptoms with all three dosages. The CGI items supported the efficacy for the 4.5-mg dose. The systemic side-effects and skin tolerability were similar between rotigotine and placebo (Stiasny-Kolster et al 2004).

A second double-blind, multi-center, dose-finding study compared five different dosages of rotigotine and placebo for the duration of 7 weeks. Efficacy parameters were the IRLS, CGI, and RLS-6. Of 371 enrolled patients with RLS, 340 were randomized and 285 patients were treated with rotigotine dosages varying from 1.125 mg up to 9.0 mg. A statistically significant and clinically relevant treatment difference compared with placebo was evident for the rotigotine dosages 2.25 mg, 4.5 mg, 6.75 mg, and 9 mg. The highest improvement on the IRLS total score was observed with 6.75 mg rotigotine (15 cm² patch) (Oertel et al 2005).

Conclusion

Rotigotine transdermal system, a new non-ergolinic dopamine agonist, was developed to provide a drug that can be applied once daily. To date, it is approved for the treatment of early Parkinson's disease as monotherapy and has been shown to be effective in the treatment of advanced-stage Parkinson's disease and RLS in several clinical trials.

The possibility of non-invasive and simple-to-use continuous dopaminergic stimulation may be a step toward minimizing complications arising from pulsatile stimulation. There are still ongoing trials of rotigotine in RLS and Parkinson's disease, and further results are expected in autumn 2006.

Disclosures

The authors are employees of the Klinikum Bremen-Ost, Teaching Hospital of the University of Goettingen, and have no affiliations or financial ties with Schwarz Pharma.

References

- Allen RP, Picchietti D, Hening WA, et al. 2003. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*, 4:101–19.
- Braun M, Cawello W, Horstmann R. 2005a. Lack of pharmacokinetic interactions between the dopamine agonist rotigotine and levodopa/carbidopa [abstract]. 16th International Congress on Parkinson's Disease and Related Disorders; 2005 June 5–9. Berlin. PS002/03
- Braun M, Cawello W, Poole K, Horstmann R. 2005b. Steady-state pharmacokinetics of rotigotine in patients with early-stage Parkinson's disease [abstract]. 9th Congress of the European Federation of Neurological Societies. 2005 Sep 17–20; Athens. P1245.
- Cawello W, Braun M, Horstmann R. 2005. Pharmacokinetics of transdermal rotigotine in subjects with impaired renal function [abstract]. 34th Annual Meeting of the American College of Clinical Pharmacology. 2005 Sep 11–13; Rockville, MD, USA. 102.
- Coleman RJ, Lange KW, Quinn NP, et al. 1989. The antiparkinsonian actions and pharmacokinetics of transdermal (+)-4-propyl-9-hydroxynaphthoxazine (+PHNO): preliminary results. *Mov Disord*, 4:129–38.
- Hansen K, Braun M, Horstmann R. 2005. Low drug-interaction potential of rotigotine [abstract]. 34th Annual Meeting of the American College of Clinical Pharmacology. 2005 Sep 11–13; Rockville, MD, USA. 101.
- Happe S, Trenkwalder C. 2004. Role of dopamine receptor agonists in the treatment of restless legs syndrome. *CNS Drugs*, 18:27–36.
- Jenner P. 2005. A novel dopamine agonist for the transdermal treatment of Parkinson's disease. *Neurology*, 65(Suppl 1):S3–5.
- LeWitt PA, Nausieda PA, Chang F, et al. 2005. Rotigotine transdermal system as adjunctive therapy to levodopa in patients with advanced-stage Parkinson's disease. Results of a randomized, double blind, placebo controlled, multicenter, multinational trial [abstract]. 9th Congress of the European Federation of Neurological Societies. 2005 Sep 17–20; Athens. SC115.
- Loschmann PA, Chong PN, Nomoto M, et al. 1989. Stereoselective reversal of MPTP-induced parkinsonism in the marmoset after dermal application of N-0437. *Eur J Pharmacol*, 166:373–80.
- Metman LV, Gillespie M, Farmer C, et al. 2001. Continuous transdermal dopaminergic stimulation in advanced Parkinson's disease. *Clin Neuropharmacol*, 24:163–9.
- Oertel WH, Beneš H, Geisler P, et al for the 34-center Rotigotine SP709 Study Group. 2005. Rotigotine patch efficacy and safety in the treatment of moderate to severe idiopathic restless legs syndrome - results from a multi-national double-blind placebo-controlled multi-center dose-finding study. *Sleep Med*, 6(Suppl 2):S159.
- Oertel WH, Quinn NP. 1997. Parkinson's disease: drug therapy. *Baillieres Clin Neurol*, 6:89–108.
- Olanow CW, Obeso JA. 2000. Preventing levodopa-induced dyskinesias. *Ann Neurol*, 47(Suppl 1):S167–76.
- Pfeiffer RF. 2005. A promising new technology for Parkinson's disease. *Neurology*, 65(Suppl 1):S6–10.
- Rascol O. 2005. Transdermal delivery of dopaminergic agents. *Neurology*, 65 (Suppl 1):S1–2.
- Reynolds NA, Wellington K, Easthope SE. 2005. Rotigotine in Parkinson's disease. *CNS Drugs*, 19:973–81.
- Stiasny K, Wetter TC, Trenkwalder C, et al. 2000. Restless legs syndrome and its treatment by dopamine agonists. *Parkinsonism Relat Disord*, 7:21–5.
- Stiasny-Kolster K, Kohlen R, Schollmayer E, et al; Rotigotine Sp 666 Study Group. 2004. Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of the restless legs syndrome: a double blind, placebo-controlled pilot study. *Mov Disord*, 19:1432–8.
- Swart PJ, De Zeeuw RA. 1992. Extensive gastrointestinal metabolic conversion limits the oral bioavailability of the dopamine D2 agonist N-0923 in freely moving rats. *Pharmazie*, 47:613–15.
- The Parkinson Study Group. 2003. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol*, 60:1721–8.
- Thorpy MJ. 2005. New paradigms in the treatment of restless legs syndrome. *Neurology*, 64(Suppl 3):S28–33.
- Timmerman W, Westerink BH, de Vries JB, et al. 1989. Microdialysis and striatal dopamine release: stereoselective actions of the enantiomers of N-0437. *Eur J Pharmacol*, 162:143–50.
- Trenkwalder C, Paulus W, Walters AS. 2005. The restless legs syndrome. *Lancet Neurology*, 4:465–75.
- Walters AS. 1995. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord*, 10:634–42.
- Watts RL, Wendt RL, Nausieda B, et al. 2004. Efficacy, safety and tolerability of the rotigotine transdermal patch in patients with early-stage, idiopathic Parkinson's disease: a multicenter, multinational, randomized, double-blind, placebo-controlled trial. *Mov Disord*, 19(Suppl 9):S258.