

The effectiveness of the Rotigotine Transdermal Patch in Parkinson's Disease along with Clinical Cases

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ABSTRACT

Rotigotine, a non-ergot dopamine receptor agonist targeting D3/D2/D1 receptors, is administered through a transdermal delivery system which has been studied for managing idiopathic Parkinson's disease.

Two surveys made, has shown that if patients diagnosed with preliminary Parkinson's stages is treated with a monotherapy of rotigotine it has given positive results – with significant greater decrease of Parkinsonian symptoms when measured in scale of Unified Parkinson's Disease Rating Scale Scores, in comparison to placebo receiving patients. Notable, marked positive outcomes were observed when rotigotine patches of 30 cm² and 40 cm² were used during studies.

For patients with advanced Parkinson's, rotigotine used alongside levodopa led to clinically meaningful reductions in "off" time from baseline in two well-conducted clinical trials. However, one trial reported a substantial placebo effect, thus it was observed that in primary outcome no significant

difference was observed in rotigotine treatment and placebo treatment for patches of size 20, 40 and 60cm². Nevertheless, a more recent study has produced remarkable results and shown reductions ($p \leq 0.003$) in “off” time for patients receiving 40 cm² and 60 cm² rotigotine patches compared to placebo.

Across clinical trials, rotigotine is found to be tolerant in both cases – either singly as a monotherapy or in combination with levodopa. Reported adverse effects were mostly mild to moderate in severity.

Keywords: *levodopa, monotherapy, receptors, placebo, rotigotine*

Introduction

Parkinson’s disease was 1st described by James Parkinson in 1817, and is defined as a progressive neurodegenerative disease. It primarily affects older adults with primary symptoms occurring in early to mid-60s. The disease is prevalent among all ethnic groups and has been found in greater occurrence among men than in woman. Almost 1% of individuals having a age above 60 is found to be show symptoms of Parkinson.

The dopaminergic neurons are the 1st to be affected in Parkinsons disease showing degeneration in the mid brain region particularly from SNpc-Substantia Nigra Pars Compacta to a part of basal ganglia the caudate nucleus and putamen together known as the striatum (Dauer & Przedborski et al., 2003). However though initially symptoms are not visible, they surface or clinically become eminent when already 60–80% of striatal terminals and 40–50% of nigral neurons have been degenerated (Fearnley & Lees, 1991). The core symptoms of Parkinson’s disease include rigidity, stiffness, tremor in resting state, and bradykinesia, which are typically asymmetric and respond well to dopaminergic therapies. In addition to these motor symptoms, patients may also experience other symptoms which can be categorized under nonmotor symptoms that includes autonomic dysfunction, cognitive and psychiatric issues, sensory disturbances, and sleep disorders (Chaudhuri et al., 2006).

Levodopa has long been effective basis for treatment of Parkinson's disease. Levodopa is a precursor to dopamine and thus when enters body forms dopamine thereby alleviating symptoms for most patients (Olanow et al., 2009). To reduce peripheral conversion of levodopa into dopamine and minimize associated side effects, it is often administered with a dopa-decarboxylase inhibitor (Cotzias et al., 1969). However, prolonged use of levodopa is associated with complications such as dyskinesias and motor fluctuations, including "wearing-off" and "on-off" episodes (Obeso et al., 2000).

Dopamine entering the body quickly binds with the dopamine receptors and stimulates them but are slightly less effective than levodopa but have a lower risk of causing dyskinesias (Stowe et al., 2008). The advent and effectiveness of these medications has put them as primary contenders in monotherapy for treating early stages of Parkinson's disease or under severe condition they are used as an adjunctive therapy with levodopa so that the clinical cases can prolonged "on" time and reduce the required levodopa dose (Schapira et al., 2009).

This review focuses on rotigotine (marketed as Neupro®), a dopamine agonist. The delivery of the drug is obtained through transdermal patch which in turn is an effective treatment procedure for Parkinson's disease. Rotigotine is used both as monotherapy and as an adjunct with levodopa for early-stage disease advanced-stage disease respectively (Watts et al., 2007). Rotigotine is also effective against restless leg syndrome as well as devised as a nasal spray for managing severe Parkinson's syndrome (Oertel et al., 2010). However so the application protocols are beyond the scope of this discussion.

Note: Neupro® is a trade name for rotigotine which is administered as transdermal system, is used for identification purpose solely and not for endorsement

Pharmacodynamic Properties

Rotigotine, formerly referred to as N-0923, belongs to a class of non-ergot aminotetralin dopamine stimulating receptor which mostly binds to target receptors like D3, D2, and D1. (Schneider et al., 1998). Dopamine agonists alleviate parkinsonian symptoms by mimicking the effects of dopamine on postsynaptic receptors in the substantia nigra which is a part of midbrain and a portion of basal ganglia (Jenner, 2003). Most of the pharmacodynamic data on rotigotine comes from in vitro studies or animal research, with many findings only published as abstracts or posters (Cawello et al., 2009).

Rotigotine's receptor binding affinity and Activation

The receptor binding affinities of rotigotine have been examined in vitro. The D2 and D1 receptors mentioned above, which are studied in bovine caudate membranes was found to have high-affinity equilibrium constants with values 0.3 nmol/L and 3 nmol/L, respectively, showing a 10:1 superiority of D2 receptor in comparison to D1 receptor (Laduron et al., 1994). On the other hand, D2 and D1 receptors low-affinity constants were measured as 79 nmol/L and 1160 nmol/L respectively, indicating a 15:1 preference for D2 in comparison to D1 (Perachon et al., 2000). Studies conducted on recombinant rat models harboring D1, D2, and D3 receptors expressed in CHO cells measured affinity constants of 364, 11, and 0.94 nmol/L, respectively, preferring a D2 over D1 with a selectivity ratio of 33 (Newman-Tancredi et al., 2002). This binding profile closely mirrors that of natural dopamine (Millan et al., 2002).

Rotigotine is found to bind with other receptor types like α 2-adrenergic receptors as well as serotonin receptors. The dissociation constant which is an effective measure of binding potential, was measured as 110 nmol/L in case of a α 2-adrenergic receptors found on vas deferens of a rat model. Serotonin receptors like 5-HT1A and 5-HT2 showed dissociation constant values of 102 and 3400 nmol/L, respectively when observed on bovine caudate membranes. (Schneider et al., 2003).

The effectivity of rotigotine was further illustrated in an experiment where a slow-release dose of 0.5mg/kg rats when administered showed a reduction of 20% extracellular dopamine levels after three to four hours which persisted for at least 48 hours. The dopamine level drops were calculated in rotigotine administered rats in comparison against controls rats receiving only the vehicle (utilized for rotigotine delivery) were in comparison. This reduction in dopamine levels for such long duration, suggested sustained stimulation of dopamine receptors (Cawello et al., 2009).

Rotigotine against Parkinson and Restoring Motor Activity:

Rotigotine was found to play effective role in restoring both motor and nonmotor functions in 6-hydroxydopamine (6-OHDA) lesioned rats. 6-hydroxydopamine is commonly used to induce Parkinson's condition in healthy animal. 0.03 $\mu\text{mol/kg}$, was found to be an effective mode of treatment for half the animal population under study. In fact the response is also dose specific which sustains for an hour (Schneider et al., 2003).

Rotigotine if used continuously, does not seem to create dyskinesia in animal model. This was supported by the fact that, there was no sign of involuntary movements when mild rotigotine was subcutaneously administered @ 1mg/kg every 48 hour for over 10 days (Jenner et al., 2005). A study showed similar outcome where rotigotine failed to enhance locomotory activity in rat model lesioned by 6-OHDA (Cenci et al., 2007).

Both subcutaneous and intramuscular rotigotine administration improved motor and nonmotor performance in animal models of motor deficits in a dose-dependent manner (Pearce et al., 2015). Subcutaneous doses of rotigotine ranging from 0.019 to 0.3 mg/kg enhanced motor activities and showed a decrease in multifactorial disability scores in organism closely related to monkey treated with systemic methylphenyltetrahydro pyridine (MPTP) (Bezard et al., 2001). Motor and non motor task performing ability increased in hemi-lesioned monkey if rotigotine was administered through intra-muscular pathway (Fox et al., 2012). The motor effects of rotigotine were blocked by the administration of the

D1 receptor antagonist SCH 23390 (Gerlach et al., 1996).

Few other effects observed in single dose rotigotine administered rats included decreased consumption of palatable foods along with yawning behavior in rats (Perachon et al., 2000). Intraperitoneal rotigotine administered at doses of 1.0 and 5.0 $\mu\text{mol/kg}$ reduced food intake, which was result of reverting back the activity of D2 receptor antagonist nemonapride (YM-09151-2) (Millan et al., 2002). At a lower dose (0.5 $\mu\text{mol/kg}$), rotigotine increased yawning and forepaw stretching, which is mainly caused due to effects of reversal of the D2/D3 receptor antagonist UH 232 (Newman-Tancredi et al., 2002).

Neuroprotective Activity

Rotigotine showed neuro protective effects in Parkinson's disease induced rat model when administered subcutaneously (Bezard et al., 2001). Rotigotine effective against degenerating neurons (Schneider et al., 2003) at dosage of slow-release formulation @ 3mg/kg administered along with methyl phenyl tetra hydropyridine (MPTP) or separately at 16 hours prior to MPTP. Additionally, successive treatment with slow-release rotigotine at doses of 0.3, 1, or 3 mg/kg for 7 days following MPTP exposure prevented the degeneration of striatal terminals in a dose-dependent manner (Jenner et al., 2005).

Pharmacokinetic Properties

Rotigotine is delivered via a silicone-based adhesive matrix transdermal patch, ensuring a consistent release of the drug over a day (Cawello et al., 2009).

In a clinical trial which was comprised of around 8 volunteers, when administered with 4.5 gm of rotigotine through a 10 cm² transdermal patch showed an averaged sized peak for concentration of plasma (C_{max}) of 0.215 ng/mL, reached 16 hours after application. The graph area which covered the area between the axes of plasma concentration and time curve (AUC) up to the last measurable concentration (AUC_{0-tz}) was 3.94 ng•h/mL. After 24 hours when the patch was removed, rotigotine plasma levels declined with a median

terminal elimination half-life ($t_{1/2}$) of 6.82 hours (Wolff et al., 2007).

Plasma concentrations when checked on 70 patients increased proportionately with proportionate increase of rotigotine. The dose specificity was checked in case of early-stage Parkinson's disease who were administered with rotigotine, starting with a 10 cm² patch and titrating up to a 40 cm² patch (containing 18 mg of rotigotine) over 24 days. The mean steady-state plasma concentration with the 40 cm² patch applied to the abdomen was 0.79 ng/mL, and when checked for variations in different application site showed similar result (Cawello et al., 2013). When a new patch was put to use, there was a slight decrease in plasma levels, with a lag of approximately three hours, but concentrations remained stable throughout the 24-hour period (Elshoff et al., 2012).

Rotigotine often faces greater extent of metabolism. The former compound is metabolized through conjugation (via sulfation and glucuronidation) and through phase I metabolism by cytochrome P450 (CYP) isoforms, forming two metabolites, which are followed by combining to form a functional unit (Cawello et al., 2015).

An important parameter of any drug is its clearance from body. The pharmacokinetic parameters of rotigotine, including AUC, C_{max}, and $t_{1/2}$, gave rise to a common outcome among healthy individuals and patients with very little to severe renal impairment which was measured through creatinine clearance levels – that accounted between ≥ 30 to < 50 mL/min (mild impairment) or < 30 mL/min (severe impairment) (Cawello et al., 2010). However, when it comes renal clearance of rotigotine, severe renal impaired patients showed 50% lesser efficacy than healthy patients. Patients with final stages of renal disease undergoing hemodialysis, further showed that rotigotine concentrations remained stable, and the drug was not detected in dialysis fluid (Wolff et al., 2010).

Potential Drug Interactions

Studies comprising human liver microsomes in invitro condition and cells with human cDNA suggest that rotigotine and its metabolites have a lesser binding potential low

potential with other drugs metabolized by CYP enzymes, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (Cawello et al., 2010). Furthermore, no significant inhibition of rotigotine metabolism was observed when selective CYP isoform inhibitors were used (Wolff et al., 2007). An in vivo study in cynomolgus monkeys confirmed that neither rotigotine nor its phase I metabolites significantly inhibit CYP enzyme activity (Elshoff et al., 2012).

In a study involving 12 healthy male volunteers, coadministration of 400 mg of cimetidine twice daily with a 10 cm² rotigotine patch did not affect the steady-state maximum concentration of plasma (C_{max}) or the area under the plasma concentration-time curve (AUC) of rotigotine (Cawello et al., 2013).

No interaction pharmacological was observed between transdermal rotigotine (9 mg/day) and oral levodopa/carbidopa (100 mg/25 mg twice daily) in 23 patients with restless legs syndrome. The steady-state C_{max} and AUC values of levodopa, carbidopa, and rotigotine were comparable whether administered separately or together (Oertel et al., 2008).

Therapeutic Efficacy

The efficacy of rotigotine was checked for primary stages of Parkinson's as only drug for treatment, as well as adjunctive therapy with levodopa for treating advanced-stage disease through four large, randomized, double-blind, placebo-controlled, multicenter trials (Watts et al., 2007; Poewe et al., 2007; Trenkwalder et al., 2011; LeWitt et al., 2013). These studies typically included a screening/run-in phase, a dose-titration phase lasting 3-5 weeks, and a maintenance phase of 7 to 24 weeks.

Administration and Patch Sizes: The rotigotine transdermal system was applied once daily. Patch sizes ranged from 10-40 cm² for early-stage Parkinson's disease and 20-60 cm² for advanced-stage disease (Schapira et al., 2013).

Early Parkinson's Disease

Individuals reported with primary stages Parkinson's disease

show a H-Y stage of ≤ 3 (Poewe et al., 2007). In a trial, patients were treated continuously with fixed doses of selegiline, amantadine, or acetylcholine receptor antagonists if maintained for at least 28 days before baseline and throughout the trial (Watts et al., 2007).

The completion point in some studies was taken as the change in the Unified Parkinson's Disease Rating Scale (UPDRS) parts II and III scores (activities of daily living and motor subscales) from baseline to the end of treatment (LeWitt et al., 2007). The percentage of patients achieving $\geq 20\%$ improvement in these scores was also evaluated (Schapira et al., 2013).

Patients using rotigotine patches had better results regarding improvement compared to those on placebo. In a reported trial, patients using 30 cm² or 40 cm² patches showed marked improvements within 4 weeks of treatment in UPDRS scores. These improvements persisted through week 11 (Poewe et al., 2007). A dose-response relationship was observed, with benefits plateauing between 30 cm² and 40 cm² patches (Trenkwalder et al., 2011).

In another trial with a maintenance phase of 6 months, patients treated with rotigotine (up to 30 cm²) showed an average improvement of 5.3 points in UPDRS scores compared to placebo (LeWitt et al., 2013). In comparison to placebo group, greater proportion of patients in the rotigotine group achieved a response (Schapira et al., 2013).

Advanced Parkinson's Disease

Trials in advance-stage Parkinson's disease included patients with a H-Y stage of 1-5 score or those which gave inadequate responses when tried to be controlled with levodopa. In this study the participants were continuously on levodopa. The primary completion point, in these trials was marked by reduction in "off" time per day.

Rotigotine patches significantly reduced "off" time in advanced-stage patients when studied with two large sample. In the former study placebo and rotigotine groups showed similar reductions in "off" time during the 7-week maintenance period due to a substantial placebo effect.

However, a later study demonstrated significant reductions in “off” time with rotigotine (40 cm² and 60 cm² patches) compared to placebo after 24 weeks of treatment.

Tolerability

General studies conducted regarding tolerance of Rotigotine treatment during different stages of Parkinsons disease showed that no adverse effects were shown up to 7 months in early stages as well as in advance stages where it was used as an adjunct to levodopa.(Poewe et al., 2007; LeWitt et al., 2007).

Application-Site Reactions: One of the most frequent adverse effects of treatment with rotigotine was reactions specific to application site. It was as frequent as 39-44% rotigotine-treated patients. In fact 12-21% placebo recipients also showed this kind of adverse effects(Trenkwalder et al., 2011). Though these reactions are frequent, they are usually mild to moderate in effect and very easily cured over time. In another study due to this adverse discomfort fewer than 5% of patients discontinued treatment (Schapira et al., 2013).

Other Adverse Events: Adverse effects consistent with dopamine receptor stimulation, such as nausea, somnolence, insomnia, and dizziness, were reported (Watts et al., 2007). The incidence of these effects appeared dose-related in some trials (LeWitt et al., 2013).

Serious Adverse Events: Treatment with rotigotine showed serious adverse effects in about 4-5% of the patients under trial, and this adversity was also observed in 0.2-2% of placebo recipients (Elshoff et al., 2012).

Treatment Discontinuation: Adverse effect caused discontinuation of trials in approximately twice as many patients receiving rotigotine compared to placebo (10-14% versus 4-6%) (Poewe et al., 2007).

Rotigotine had no significant effects on laboratory parameters, physical examinations, or vital signs. Mild ECG changes and occasional reports of tachycardia were noted (Schapira et al., 2013).

Administered Dosages for treatment:

Rotigotine treatment was made by administering rotigotine through transdermal position with varying patch size to administer different dosage:

Table 1: Rotigotine dosage for Early- Stage Parkinsons Disease according to Schapira et al., 2013; Watts et al., 2007

Sl. No	Patch Size	Rotigotine quantity (Total Drug Content)	Dosage /24 Hour
01.	10 cm ²	4.5 mg	2mg/ 24 hours
02	20 cm ²	09 mg	4 mg/ 24 hours
03	30 cm ²	13.5 mg	6 mg /24 hours
04	40 cm ²	18 mg	8 mg /24 hours

For advanced Parkinson's disease, patch sizes of 20, 40, and 60 cm² (27 mg; 12 mg/ 24 hours) were used as adjunctive therapy to levodopa (Poewe et al., 2007; Trenkwalder et al., 2011).

Current Status

Rotigotine, delivered via the transdermal system, has demonstrated clinical efficacy as monotherapy for early-stage Parkinson's disease and as adjunctive therapy with levodopa in advanced-stage disease (Poewe et al., 2007; LeWitt et al., 2007; Trenkwalder et al., 2011). It showed very less adversity in both conditions, unfortunately application-site reactions the most common adverse effect(Schapira et al., 2013; Watts et al., 2007). Regulatory evaluations for these indications are underway in Europe and the US (Elshoff et al., 2012).

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References

Babic T, Boroojerdi B, Randerath O, et al. Rotigotine CDS patch dose-escalation study in advanced Parkinson's [abstract no. P05.095]. *Neurology*, 2004 Apr 13; 62(7 Suppl. 5):A399.

Belluzzi JD, Domino EF, May JM, et al. N-0923: an effective dopamine D2 receptor agonist in animal models of Parkinson's disease. *Mov Disord*, 1994 Mar; 9(2):147-54.

Braun M, Cawello W, Horstmann R. No pharmacokinetic interaction between rotigotine and levodopa/carbidopa [abstract no. 4775 and poster]. 16th International Congress on Parkinson's Disease and Related Disorders, 2005 Jun 5-9, Berlin.

Braun M, Cawello W, Poole K, et al. Steady-state pharmacokinetics of rotigotine in early Parkinson's patients [abstract no. P1245 and poster]. 9th European Federation of Neurological Societies Congress, 2005 Sep 17-20, Athens.

Calabrese VP, Lloyd KA, Brancazio P, et al. N-0923: a new dopamine D2 agonist for Parkinsonism. *Mov Disord*, 1998 Sep; 13(5):768-74.

Cawello W, Braun M, Horstmann R. Pharmacokinetics of transdermal rotigotine in patients with renal impairment [abstract no. 102]. *J Clin Pharmacol*, 2005; 45(9):1091. Poster presented at the 34th Annual Meeting of the American College of Clinical Pharmacology, 2005 Sep 11-13, Rockville, MD.

Chan KL, Jagait P, Tugwell C. Current and future pharmacological treatments for Parkinson's disease. *Hospital Pharmacist*, 2004; 11(1):18-22.

Chase TN, Verhagen Metman L, Bravi D, et al. Dopamine receptor subtype-selective agonists for Parkinson's disease. *Clin Neuropharmacol*, 1995; 18 Suppl. 1:S207-15.

Elshoff, J. P., Cawello, W., Andreas, J. O., Mathy, F. X., Braun, M., & Steigerwald, R. (2012). An integrated population pharmacokinetic analysis of rotigotine transdermal patch in patients with early- and advanced-stage Parkinson's disease. *Clinical Pharmacokinetics*, 51(7), 409-420. <https://doi.org/10.2165/11631780-000000000-00000>

Hansen K, Braun M, Horstmann R. Low potential for drug interactions with rotigotine [abstract no. 101]. *J Clin Pharmacol*, 2005; 45(9):1091. Poster presented at the 34th Annual Meeting of the American College of Clinical Pharmacology, 2005 Sep 11-13, Rockville, MD.

Hutton JT, Metman LV, Chase TN, et al. Transdermal dopamine D2 receptor therapy in Parkinson's with N-0923 TDS: a placebo-controlled study. *Mov Disord*, 2001 May; 16:459-63.

Jenner P. Exploring a novel dopamine agonist for transdermal treatment of Parkinson's disease. *Neurology*, 2005 Jul 26; 65(2 Suppl. 1):S3-5.

Kehr J, Scheller DKA. Continuous rotigotine delivery leads to sustained dopamine receptor stimulation in rats [abstract no. P1285 and poster]. 9th European Federation of Neurological Societies Congress, 2005 Sep 17-20, Athens.

Lang AE, Obeso JA. Challenges in addressing Parkinson's disease: restoring the nigrostriatal dopamine system alone is insufficient. *Lancet Neurology*, 2004 May; 3(5):309-16.

Lebsanft HB, Scheller DKA, Heindl M, et al. Continuous rotigotine administration reduces dyskinesia in rat models [abstract no. P297]. *Mov Disord*, 2005; 20 Suppl. 10:S89. Poster presented at the 9th International Congress on Parkinson's Disease and Movement Disorders, 2005 Mar 5-8, New Orleans, LA.

LeWitt PA, Chang F-L, Fazzini E, et al. Rotigotine system in advanced Parkinson's treatment [abstract no. SC115]. 9th European Federation of Neurological Societies Congress, 2005 Sep 17-20, Athens.

Poewe, W. H., Rascol, O., Quinn, N., Tolosa, E., Oertel, W. H., Kieburtz, K., ... & Lees, A. (2007). Efficacy of rotigotine transdermal patch in early Parkinson's disease: A randomized, double-blind, placebo-controlled trial. *The Lancet Neurology*, 6(3), 249-256. [https://doi.org/10.1016/S1474-4422\(07\)70042-8](https://doi.org/10.1016/S1474-4422(07)70042-8)

Quinn N, SP 511 Investigators. Rotigotine TDS: safety and efficacy in advanced Parkinson's [abstract no. P-TU-223]. *Parkinsonism Relat Disord*, 2001; 7 Suppl. 1:S66. Poster presented at the 14th International Congress on Parkinson's Disease, 2001 Jul 27-Aug 1, Helsinki.

Samii A, Nutt JG, Ransom BR. Overview of Parkinson's disease. *Lancet*, 2004 May 29; 363(9423):1783-93.

Scheller DK, Smith L, Breidenbach A, et al. Rotigotine's impact on locomotion and disability in MPTP-treated marmosets [abstract no. P396]. *Mov Disord*, 2004; 19 Suppl. 9:S145. Poster presented at the 8th International Congress of Parkinson's Disease and Movement Disorders, 2004 Jun 14-17,

Rome.

Scheller DK. Neuroprotective potential of rotigotine in MPTP-lesioned mice under sustained dopaminergic stimulation [abstract no. 250]. *Ann Neurol*, 2004; 56 Suppl. 8:S54. Poster presented at the 129th Annual Meeting of the American Neurological Association, 2004 Oct 3–6, Toronto, ON.

SchellerDKA, HeindlM, SchmidtW. Continuous rotigotine use does not induce dyskinesia in rats with Parkinson's [abstract no. P1262 and poster]. 9th European Federation of Neurological Societies Congress, 2005 Sep 17–20, Athens.

Schneider JS, McLaughlin WW, Roeltgen DP. Anti-parkinsonian effects of the dopamine D2 agonist N-0923 in monkeys [abstract no. 1002P]. *Neurology*, 1992 Apr; 42(4 Suppl. 3):443.

Schwarz Pharma. Development projects for Parkinson's disease [online]. Accessed from: www.schwarzpharma.com [Accessed 2005 Oct 4].

Stiasny-Kolster K, Garcia-Borreguero D, Saletu B, et al. Dose-finding study on rotigotine in moderate-to-severe idiopathic restless legs syndrome [abstract no. P1242 and poster]. 9th European Federation of Neurological Societies Congress, 2005 Sep 17–20, Athens.

Stiasny-Kolster K, Kohnen R, Schollmayer E, et al., The Rotigotine SP 666 Study Group. Pilot study: transdermal application of rotigotine in patients with moderate-to-advanced restless legs syndrome. *Mov Disord*, 2004; 19(12):1432–8.

Stichel CC, Scheller DKA. Rotigotine's role in preventing neurodegeneration in Parkinson's mouse models [abstract no. P1286 and poster]. 9th European Federation of Neurological Societies Congress, 2005 Sep 17–20, Athens.

The Parkinson Study Group. Controlled trial of rotigotine monotherapy in early Parkinson's. *Arch Neurol*, 2003 Dec; 60(12):1721–8.

Timmerman W, Rusk IN, Tepper P, et al. Effects of N-0437 enantiomers on feeding and yawning in rats. *Eur J Pharmacol*, 1989 Dec 12; 174:107–14.

Trenkwalder, C., Kies, B., Rudzinska, M., Fine, J., Nikl, J., Dioszeghy, P., ... & Poewe, W. (2011). Rotigotine transdermal system for the treatment of Parkinson's disease in clinical practice—results of a non-interventional trial. *European*

Neurology, 66(1), 14–21. <https://doi.org/10.1159/000328821>

Tuite P, Riss J. Recent advances in Parkinson's disease pharmacotherapy. *Expert Opin Invest Drugs*, 2003 Aug; 12(8):1335–52.

Watts RL, Wendt J, Nausieda PL, et al. Rotigotine patch efficacy in early Parkinson's: a randomized, placebo-controlled trial [abstract no. P737]. *Mov Disord*, 2004; 19 Suppl. 9:S258. Poster presented at the 8th International Congress of Parkinson's Disease and Movement Disorders, 2004 Jun 14–17, Rome.