

Review of Rotigotine for Parkinson Disease

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Parkinson disease (PD) is a progressive neurodegenerative disorder that affects an estimated 1.5 million people in the United States with an estimated 60,000 new cases being diagnosed each year.² While the condition usually develops after the age of 65, 15% of those diagnosed are under 50 years of age. Parkinson disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and, in extreme cases, a loss of physical movement (akinesia).³ Motor fluctuations experienced by patients are characterized by alternating periods of improved motor function, referred to as “on” periods, and poor or absent motor function, referred to as “off” periods. In late stages of the disease, dyskinesias may also be present. The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. The medications most commonly used to treat PD attempt to either replace or mimic dopamine, which improves the tremor, rigidity and slowness associated with Parkinson disease.

PHARMACOLOGY/PHARMACOKINETICS

Rotigotine is a non-ergoline D₃/D₂/D₁ dopamine agonist for the treatment of Parkinson disease.¹ The precise mechanism of action of rotigotine as a treatment for Parkinson disease is unknown although it is thought to be related to its ability to stimulate dopamine D₂ receptors within the caudate-putamen in the brain. Rotigotine is delivered via a thin, matrix-type transdermal system composed of three layers. On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 mg/cm²), independent of patch size. Similar absorption per cm² was observed in healthy subjects and in patients with early stage Parkinson disease. Rotigotine is primarily eliminated in the urine as inactive conjugates. The pharmacokinetic profile showed biphasic elimination with an initial half-life of three hours. After removal of the patch, plasma levels decreased with a terminal half-life of five to seven hours.

No dosage adjustments are required in renal or hepatic insufficiency, however in subjects with severe renal impairment not on

Summary

Indication. Rotigotine (Neupro®, Schwarz Pharma) is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson disease.¹

Monitoring Parameters. Both sitting and standing blood pressure should be monitored, especially at the beginning of treatment, due to the risk of orthostatic hypotension with dopamine agonists. Monitor for drowsiness, as sleep attacks or sudden onset of sleep during activities of daily living, including while driving, have been reported with rotigotine transdermal patch use. Monitor for signs of an application site reaction as this was the most common adverse event leading to the discontinuation of treatment in clinical trials. Weight gain is often associated with fluid retention which may be a cause of concern in patients with congestive heart failure or renal insufficiency. Periodic skin examinations for melanoma should be performed by qualified individuals.

Dose. Rotigotine should be initiated at a dose of 2 mg/24 hours. Dose may be increased weekly by 2 mg/24 hours if tolerated and if additional therapeutic effect is needed. The lowest effective dose in clinical trials was 4 mg/24 hours. The highest recommended dose is 6 mg/24 hours. Doses above 6 mg/24 hours have not shown any additional therapeutic benefit and are associated with an increased incidence of adverse reactions. If it becomes necessary to discontinue rotigotine, the dose should be reduced gradually by 2 mg/24 hours every other day, until complete withdrawal.

Geriatrics. Plasma concentrations of rotigotine in patients 65 to 80 years of age were similar to those observed in younger patients. Although not studied, exposures in older subjects (>80 years) may be higher due to skin changes with aging.

Pregnancy. Pregnancy Category C. There are no well-controlled studies in pregnant women. Rotigotine should only be used during pregnancy if the potential benefits justify the risk to the fetus.

Breastfeeding. Rotigotine decreases prolactin secretion in humans and could potentially inhibit lactation. It is not known whether rotigotine is excreted in human breast milk. Because of the possibility that rotigotine may be excreted in human milk, and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Renal Insufficiency. No dosage adjustment is recommended in patients with renal dysfunction. The effect of renal function on rotigotine pharmacokinetics has been studied in subjects with mild to severe impairment of renal function including subjects requiring dialysis compared to healthy subjects. There were no relevant changes in rotigotine plasma concentrations. In subjects with severe renal impairment not on dialysis, (i.e., creatinine clearance 15 to <30 mL/min), exposure to rotigotine conjugates was doubled; however, this was determined to be clinically insignificant.

Hepatic Impairment. No dose adjustment is necessary in patients with moderate impairment of hepatic function (Child Pugh classification – Grade B). The pharmacokinetics of rotigotine have not been studied in patients with severe hepatic impairment.

Cost. The monthly cost of rotigotine therapy based on AWP, assuming a 30 day month, would be \$84.30 for a patient maintained on the 2 mg/24 hours system, or \$288.90 for a patient maintained on either the 4 mg/24 hours or 6 mg/24 hours system.

dialysis, (i.e., creatinine clearance < 30 to 15 mL/min), exposure to rotigotine conjugates is doubled.¹ This exposure has not been found to be clinically significant.

When single doses of 40 cm² systems are applied to the trunk, there is an average lag time of approximately three hours until drug is detected in plasma, (range one to eight hours).¹ Minimum plasma concentrations most commonly occur between zero to seven hours post dose. Maximum plasma concentrations occur between 15 to 18 hours post dose, but can occur anywhere from four to 27 hours post dose. Over a daily dose range of 2 mg/24 hours to 8 mg/24 hours, it has been found that rotigotine plasma concentrations are proportional to the dose of medication used. In clinical studies, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm) and the mean measured plasma concentrations of rotigotine were stable over the six months of maintenance treatment. Differences in bioavailability for the different application sites at steady-state ranged from less than 1% (abdomen vs. hip) to 64% (shoulder vs. thigh) with shoulder application showing higher bioavailability. These differences have not been found to be clinically significant.

ASSESSMENT OF THE EFFECTIVENESS OF PARKINSON DISEASE MEDICATIONS

The Unified Parkinson's Disease Rating Scale (UPDRS) was developed in 1987 by a team of investigators as an overall assessment scale that would quantify the signs and symptoms of Parkinson disease.^{4,5} It allows for an overall measure of disability and individual subscores, and includes both scoring by a clinician (motor examination) and a historical report of mental functioning and activities of daily living (ADL) obtained by questioning the patient. The UPDRS has been used broadly in the last 20 years and is the most commonly used tool to evaluate new treatments for Parkinson disease. Symptomatic worsening/improvement of Parkinson disease symptoms are measured as a change from baseline. An increasing (positive) score is an indicator of worsening Parkinson disease symptoms and a decreasing (negative) score indicates an improvement in Parkinson disease symptoms.

Hoehn and Yahr staging is another tool used by investigators to assess Parkinson disease severity.⁶ Hoehn and Yahr staging separates Parkinson disease into five stages based on symptom severity, degree of disability, and whether symptoms are one-sided or bilateral in their presentation. Stage 1 represents one-sided symptoms that are mild in their presentation with minimal disability whereas stage 5 represents invalidism, where the patient can no longer stand or walk and requires constant nursing care. Hoehn and Yahr staging has been largely replaced by the more complicated UPDRS.

CLINICAL TRIALS

Early-Stage Parkinson Disease

The Parkinson Study Group conducted a randomized, multicenter, double-blind, placebo-controlled, parallel group, dose-ranging study to determine the efficacy, safety, and tolerability of rotigotine in patients with early Parkinson disease who were not yet receiving dopaminergic therapy.⁷ A total of 242 patients

were randomized to one of five treatment groups: placebo, 4.5 mg rotigotine patch, 9 mg rotigotine patch, 13.5 mg rotigotine patch, or 18 mg rotigotine patch in equal numbers. Patients with early stage, idiopathic Parkinson disease were recruited from 36 study sites. Included were men and women older than 30 years of age who were diagnosed as having idiopathic Parkinson disease and had a Hoehn and Yahr stage of 3 or less. Subjects were permitted to take selegiline, amantadine, or anticholinergic agents if maintained at stable dosages for 28 days before baseline assessment and throughout the trial. Patients were excluded from study participation if they had cognitive impairment defined by a Mini-Mental State Examination score of less than 24; were unable to appropriately apply and remove the patches; had a history of skin sensitivity to adhesives or to other transdermal medications; had taken a dopamine agonist or levodopa within 28 days of the baseline visit or had ever taken levodopa for longer than six months; had an atypical parkinsonian syndrome; had a clinically unstable medical or psychiatric condition; had cardiac abnormalities such as arrhythmias, conduction blocks, congestive heart failure, QT-corrected interval of 500 milliseconds or more, unexplained syncope, symptomatic orthostatic hypotension, or a recent myocardial infarction; or had recent exposure to monoamine oxidase type A inhibitors, amphetamines, dopamine-depleting antihypertensive agents, neuroleptics, or antipsychotics or antiemetics that blocked central dopamine activity.

The study included a four-week maximum screening period, during which the last four to seven days included a placebo patch run-in period, a four-week double-blind dose titration period, a seven-week dose maintenance phase, a one-week de-escalation period, and a two-week safety follow-up period without study drug. The placebo patch run-in period was used to ensure that subjects could apply and remove patches appropriately and to evaluate subjects for any immediate cutaneous hypersensitivity reactions. Following the completion of all baseline requirements, subjects were randomized and instructed on the correct placement of patches. Active patches contained 4.5 mg of rotigotine per patch and were identical to the placebo patches. All subjects were instructed to wear four patches that contained various combinations of placebo and active drug and were applied once daily on the abdomen in a rotating scheme. Baseline demographic and clinical variables were similar among the five treatment groups. All subjects, except those taking placebo, began active treatment at 4.5 mg (delivered dose = 2 mg/24 hours); doses were adjusted weekly by increments of 4.5 mg. Active drug starting times were staggered so that all subjects reached their maintenance dosage at the fourth week of the titration phase. A maximum of two dosage reductions were permitted for intolerable adverse effects during weeks two through four of the dosage titration period. Subjects who required dosage reductions were not re-challenged with higher dosages of study drug. Subjects were seen at the study centers for screening, baseline, week two, week four, week seven, week 11, and week 14 visits. At randomization and at all follow-up visits, the investigator rated subjects using the UPDRS, including the mental, activities of daily living (ADL), and motor components. Hoehn and Yahr stage was determined at screening, baseline, week four, and week 11. Subjects were assessed for adverse events at each visit, and the skin was examined for applica-

tion site reactions. Medication compliance was determined at all follow-up visits by counting the unused patches returned by the subjects.

The primary endpoint was the change in the sum of the UPDRS parts II and III (ADL and motor components) between baseline and the week 11 visit. Secondary outcomes assessed included changes in the UPDRS mental, ADL, and motor component subscale scores. Safety was also assessed with measurement of changes in vital signs, ECGs, and clinical laboratory values that occurred after the study began and the severity and frequency with which adverse reactions occurred.

The mean (SD) changes from baseline to week 11 in the combined motor and ADL UPDRS score by intention-to-treat analysis for each group are presented in Table 1. These results are comparable to those patients who completed the study. Treatment effects at week 11 were statistically significant in the 13.5 mg and 18 mg groups ($p < 0.006$), and a dose-response relationship

was evident from 4.5 mg to 13.5 mg. The mean changes from baseline to week 11 in the ADL, motor, and combined ADL and motor component subscale scores for those patients completing the study are presented in Table 2.

There were statistically significant improvements noted in the sum of the motor and ADL UPDRS subscale scores by the week four visit and these improvements were sustained throughout the maintenance phase. Following the withdrawal of medication, these subscale scores returned to prior baseline values. There was a plateau in therapeutic effect that occurred between the 6 mg/24 hours and 8 mg/24 hours dose while the incidence of adverse events increased.

Overall 91% of patients experienced at least one side effect. Nausea, application site reactions, dizziness, somnolence, insomnia, vomiting, and fatigue occurred more commonly in patients assigned to the rotigotine treatment groups. It was determined that 35% of the application site reactions occurred in patients while they were using placebo patches. The percentage of patients completing the study based on their originally assigned dose is presented in Table 3. The compliance rate was determined to be approximately 97.5% in all five treatment groups. In all, thirty-six patients withdrew from this study prior to its completion, with no statistically significant difference identified between treatment groups. The occurrence of adverse events was the most common reason for patient withdrawal, with skin reactions being the most common adverse event.

Watts et al conducted a Phase III randomized, multicenter, double-blind, placebo-controlled, two-arm, parallel-group study to compare safety and efficacy of the once daily rotigotine transdermal patch to placebo in early-stage Parkinson disease.⁸ A total of 277 patients were randomized to receive placebo ($n=96$) or rotigotine ($n=181$) starting at 2 mg/24 hours titrated weekly up to 6 mg/24 hours, and then maintained for six months. Patients with early-stage, idiopathic Parkinson disease were recruited from 50 clinical study sites located in the U.S. and Canada. Patients were enrolled if they were 30 years of age or older and had a diagnosis of idiopathic Parkinson disease of less than or equal to five years in duration, a UPDRS Motor Function Examination (part III) score of at least 10 at baseline, a Hoehn and Yahr stage score less than or equal to 3, two or more of the cardinal signs of Parkinson disease (bradykinesia, resting tremor, rigidity, or postural instability), a Mini-Mental State Examination score of 25 or more, and if no other known or suspected cause of parkinsonism was identified. Patients previously receiving an

TABLE 1. CHANGE IN SUM OF UPDRS SCORES

Treatment Groups	Change in sum of UPDRS scores	Standard Deviation
Placebo	-0.29	± 7.66
Rotigotine transdermal patch (dose delivered)		
4.5 mg (2 mg/24 hour)	-1.2	± 6.53
9 mg (4 mg/24 hour)	-3.13	± 6.37
13.5 mg (6 mg/24 hour)	-5.08	± 7.03
18 mg (8 mg/24 hour)	-5.3	± 7.02

TABLE 2. CHANGE IN ADL, MOTOR, AND ADL AND MOTOR COMPONENT SUBSCALE SCORES

Rotigotine transdermal patch (dose delivered)	Difference in mean change between active group and a placebo group (95% CI)*	p value
ADL Score		
4.5 mg (2 mg/24 hour)	-0.04 (-1.05 to 0.97)	0.94
9 mg (4 mg/24 hour)	-0.84 (-1.87 to 0.18)	0.11
13.5 mg (6 mg/24 hour)	-0.92 (-1.95 to 0.11)	0.08
18 mg (8 mg/24 hour)	-1.56 (-2.57 to -0.56)	0.003
Motor Score		
4.5 mg (2 mg/24 hour)	-0.9 (-3.20 to 1.40)	0.44
9 mg (4 mg/24 hour)	-1.88 (-4.22 to 0.45)	0.11
13.5 mg (6 mg/24 hour)	-3.91 (-6.26 to -1.53)	0.001
18 mg (8 mg/24 hour)	-3.82 (-6.12 to -1.53)	0.001
ADL and Motor Score		
4.5 mg (2 mg/24 hour)	- 0.91 (-3.71 to 1.88)	0.52
9 mg (4 mg/24 hour)	- 2.78 (-5.62 to 0.06)	0.06
13.5 mg (6 mg/24 hour)	- 4.83 (-7.68 to -1.97)	0.001
18 mg (8 mg/24 hour)	- 5.23 (-8.02 to -2.44)	< 0.001

* These scores are adjusted for the baseline value of the outcome variable. Negative values indicate improvement.

TABLE 3. PERCENT OF PATIENTS COMPLETING STUDY

Treatment Groups	Percent of patients completing the study	p value
Placebo	83	
Rotigotine Transdermal System Dose (dose delivered)		
4.5 mg (2 mg/24 hour)	69	0.09
9 mg (4 mg/24 hour)	60	0.01
13.5 mg (6 mg/24 hour)	65	0.04
18 mg (8 mg/24 hour)	75	0.22

anticholinergic agent, monoamine oxidase-B inhibitor, or an *N*-methyl-D-aspartate antagonist, such as amantadine, had to have been on a stable dose for at least 28 days at study baseline and had to be maintained at the same dose for the duration of the study. Exclusion criteria included: prior or concurrent therapy with a dopamine agonist or carbidopa/levodopa within 28 days of study baseline visit; carbidopa/levodopa therapy lasting for more than 6 months since diagnosis; atypical parkinsonism; a history of surgical intervention for Parkinson disease; clinically relevant hepatic, renal, or cardiac dysfunction; a diagnosis of epilepsy; a history of seizures as an adult; stroke or a TIA within the last year; significant skin hypersensitivity to adhesive or other transdermal products or recent unresolved contact dermatitis; known intolerance/hypersensitivity to the antiemetic ondansetron; pregnancy or nursing; and inadequate birth control methods. Patients receiving CNS active therapy were excluded, unless their medication dose(s) had been stable for at least 28 days prior to baseline and were likely to remain stable for the duration of the trial.

Following the completion of screening assessments which included 12-lead ECG, hematology and serum chemistry, urinalysis, neurological assessments, physical exam, and training on patch application, patients were randomized in a 2:1 ratio to receive either rotigotine or placebo. Baseline characteristics were similar among treatment groups. Dosing was initiated at 2 mg/24 hours and weekly, doses were titrated by 2 mg/24 hours per week, to a maximum dose of 6 mg/24 hours. The optimal dose for each subject was defined as the dose that resulted in maximal reduction of parkinsonian symptoms without intolerable side effects. If patients experienced intolerable side effects, they were allowed to “back titrate” to the previous week’s dose. After achieving the optimal dose, patients began a 24-week maintenance phase. Patients were evaluated every four weeks. At the end of the 24-week maintenance phase, the dose was titrated down with a dose reduction every two days until the patient reached the lowest dose, 2 mg/24 hours, for two days, at which point treatment was completely stopped. Patients were asked to return to the clinic for a follow-up visit 28 days after the end of treatment. Patients who had completed maintenance treatment were offered the option to enroll in an open-label extension trial.

The primary endpoint measures were the change in the UPDRS scores (parts II and III) from baseline to the end of the maintenance phase, and responder rates (patients with $\geq 20\%$ decrease in the sum of the UPDRS scores from parts II and III from baseline to the end of maintenance treatment). Compliance with the medication treatment regimen was assessed. Safety assessments were also completed during the trial. Spontaneous reports of adverse effects from both patients and investigators were assessed in terms of severity, outcome, and suspected causality.

At the time of completion of the study-drug titration phase, patients receiving rotigotine had experienced greater UPDRS score improvements than those receiving placebo. At the end of the six-month maintenance phase, patients receiving rotigotine continued to have improved UPDRS scores, while those patients who had been receiving placebo had poorer UPDRS scores compared with baseline. Differences between the mean increase in UPDRS subtotal scores as well as the proportion of responders are presented in Table 4. Superior improvement in the Motor Examination (part III) of the UPDRS was the greatest contributor for the rotigotine group’s subtotal improvements, as the mean change in motor scores from baseline to the end of the maintenance phase was $-3.5 (\pm 7.26)$ and the mean change in UPDRS part II score was $-0.3 (\pm 3.54)$. Patients in the rotigotine treatment group demonstrated a 25-30% improvement in their UPDRS scores from baseline to the end of the maintenance treatment phase.

Compliance with the medication regimen was similar between the two treatment groups, with a 98% compliance rate demonstrated by patients in the rotigotine treatment group and 100% compliance rate in the placebo-treated group.

The majority of adverse effects reported were assessed to be mild to moderate in severity. Nausea, drowsiness, dizziness, and headache were more commonly reported in patients in the rotigotine treatment group vs. those in the placebo treatment group. Overall, 14% of patients in the rotigotine treatment group experienced adverse effects that resulted in discontinuation of the drug therapy as compared to 6% in the placebo treatment group. Application site reaction was the most common adverse effect that led to discontinuation.

Jankovic et al completed a subgroup analysis of the same study population to assess the effects of rotigotine therapy on Clinical Global Impression Scale rating, prolactin concentrations, rotigotine plasma concentrations, quality of life (QOL) measurements, and Epworth Sleepiness Scale (ESS) scores.⁹

At the end of the maintenance phase, the percentage of patients in the rotigotine treatment group that achieved improvement in Clinical Global Impression Scale scores was significantly higher than those treated with placebo (57% vs. 30%, $p < 0.001$). Prolactin serum levels decreased from baseline to the end of the maintenance phase in those patients being treated with the 6 mg/24 hour rotigotine transdermal system as outlined in Table 5. During the titration period, the mean plasma concentrations of rotigotine increased proportionally to the dose, up to 0.76 ng/mL at a dose of 6 mg/24 hours. These plasma concentrations remained stable during the maintenance period, with no statistically significant difference in plasma concentrations seen between those measured before transdermal patch removal and those measured one to four hours after a new transdermal patch was applied.

TABLE 4. DIFFERENCES IN UPDRS SUBTOTAL SCORES AND RESPONDER RATES

Treatment Groups	UPDRS (Part II and III) Subtotal Scores	% of Responders	Standard Deviation	p value
Placebo	1.31	19	± 0.956	< 0.0001
Rotigotine	-3.98	48	± 0.707	< 0.0001

TABLE 5. PROLACTIN CONCENTRATIONS

Treatment Groups	Baseline: Mean Prolactin Concentration (ng/mL)	Maintenance Phase: Low Prolactin Concentration (ng/mL)	Maintenance Phase: High Prolactin Concentration (ng/mL)	End of Maintenance Phase: Prolactin Concentration (ng/mL)
Placebo	6.6	6.4	7.7	
Rotigotine 6 mg/24 hour	6.8	4.8	5.4	5

In addition to the QOL components of the UPDRS, investigators also utilized the EQ-5D questionnaire (EuroQOL group) to assess the overall QOL of patients involved in the study. The EQ-5D provides a simple descriptive profile and a single index value for QOL on a 0-1 scale, with 0 representing no QOL and 1 representing an ideal QOL. The mean EQ-5D index value in the rotigotine group was 0.83 (range, 0.31 - 1; $p > 0.05$), which investigators stated showed a slight improvement from baseline that was not statistically significant. In the placebo group the mean EQ-5D index value was 0.77 (range, 0.38 - 1), which investigators assessed as a deterioration from baseline. Without baseline data however, it is difficult to know the degree of improvement or deterioration that took place.

In addition to the adverse effects previously reported by Watts et al, the subgroup analysis included an assessment of the ESS scores. At baseline, ESS scores were similar between both treatment groups. At the end of the maintenance phase, mean ESS scores increased in patients in the rotigotine treatment group and decreased in the placebo group; the difference did reach statistical significance ($p < 0.005$).

Giladi et al conducted a randomized, multicenter, multinational, double-blind, double-dummy, placebo- and ropinirole-controlled study to assess the efficacy and safety of rotigotine in patients with early stages of Parkinson disease.¹⁰ A total of 561 patients were randomly assigned in a 2:2:1 ratio to receive rotigotine ($n=215$), ropinirole ($n=228$), or placebo ($n=118$). The baseline demographics as well as the clinical variables between the treatment groups were similar. Patients that were eligible for the study had to be 30 years of age or older and have a diagnosis of Parkinson disease that was mild to moderate in severity as defined by the UK Brain Bank Criteria and Hoehn and Yahr clinical staging score of 3 or less, and a score of 10 or greater on the motor examination section (Part III) of the UPDRS. Patients were allowed to take other medications including selegiline, amantadine, anticholinergic agents or other CNS active drugs if their doses had been stable for 28 days prior to the start of the study and throughout the course of the study. Patients were excluded from the study if they had a Mini-Mental State Examination score < 25 ; a psychiatric or cognitive condition that was clinically important; were unable to apply and remove the patches correctly; had a history of skin sensitivity to adhesives or other transdermal medications; had received levodopa or a dopamine agonist within 28 days of the initial visit or had ever taken levodopa for more than 6 months; had hepatic, renal, or cardiac dysfunction that was felt to be clinically important; had an average QT_c interval of ≥ 470 ms for women and ≥ 450 ms for men as measured with three electrocardiograms that were carried out at the initiation of the study; had symptomatic orthostatic

hypotension; or had recent exposure to monoamine oxidase type A inhibitors or neuroleptics.

Following the assessment phase of the study, patients were randomized to receive rotigotine, ropinirole, or placebo. Placebo patches and capsules looked similar to the active medications used in the study. During the entire maintenance phase, patients were required to take capsules three times a day and apply two patches daily. The dose that was most effective or the maximum allowed dose was reached through titration. All of the patients randomized to the transdermal rotigotine group started their active treatment at 2 mg/24 hours with adjustments of 2 mg/24 hours made weekly, to a maximum allowed dose of 8 mg/24 hours. Patients that were randomized to the ropinirole group started active treatment at 0.25 mg orally three times daily with weekly dose adjustments of 0.25 mg three times daily for the first four weeks of therapy, then a dose increase of 1.5 mg/day on a weekly basis for four weeks, and finally a dose increase of 3 mg/day on a weekly basis for five weeks. Ropinirole had a maximum allowed dose of 24 mg/day, which is the maximum FDA-approved dose for both early-stage and advanced Parkinson disease. Thirteen weeks were needed to titrate medication doses to the maximum dose of ropinirole and four weeks were needed to titrate to the maximum dose of rotigotine. Patients in the study were allowed to back titrate the dose of study medication just once for intolerable side effects. The optimal dose was defined by the patient and investigator. If it was determined by the investigator that a patient was not going to benefit from an increased dose, the current dose was determined to be optimal. If it was determined that an increased dose was needed, titration would continue. After titration was completed, or optimal clinical benefit was achieved, the patient was maintained on that dose for a 24-week period. In the rotigotine group, 92% of patients ultimately received the maximum dose of 8 mg/24 hours. The median dose of ropinirole was 14.1 mg/day, and 26% of the patients in the ropinirole group were given the maximum dose of 24 mg/day.

The primary endpoint was the proportion of patients that responded to treatment. Patients with a $\geq 20\%$ decrease in the sum of the UPDRS Parts II (activities of daily living; ADL) and Part III (motor) scores when comparing their first visit to the end of the maintenance period were considered responders. Secondary endpoints included absolute changes in UPDRS II + III scores from the initial visit to the end of the maintenance period, changes in the UPDRS part II and III subscale scores, and demonstration of non-inferiority to ropinirole.

A significantly higher proportion of responders (52%) were found in the rotigotine group compared with placebo (30%; $p < 0.0001$). In the ropinirole arm, the responder rate was 68%

($p < 0.0001$ compared with placebo). Significant improvement in the absolute changes in the UPDRS II + III scores was found in patients in the rotigotine group. Study results are outlined in Table 6. Patients receiving rotigotine experienced an improvement in average UPDRS part II and III subscale scores from baseline to the end of treatment, by 2.1 and 5.2 respectively, and by 0.1 and 2.1 in patients receiving placebo. The investigators were unable to show noninferiority between the rotigotine transdermal patch and ropinirole. This study did not possess the necessary power to show that either of the active treatments was superior to the other treatment.

Similar adverse events were noted for patients treated with the rotigotine transdermal patch and those treated with ropinirole, except for application site reactions. Adverse events occurring more commonly among patients treated with rotigotine than those receiving placebo included nausea, vomiting, somnolence, dizziness, headache, and application site reactions. Application site reactions were considered mild to moderate in severity in 98% of cases and resolved upon removal of the patch. It is important to note that nausea, dizziness, and somnolence were observed with less frequency in patients treated with the rotigotine transdermal patch than with ropinirole.

TABLE 6. ABSOLUTE CHANGES IN THE UPDRS II + III SCORES

Treatment Groups	Decrease in the UPDRS parts II + III Subtotal Scores	Standard Deviation	p value
Placebo	-2.2	± 9.9	< 0.0001
Rotigotine	-7.2	± 10.2	< 0.0001
Ropinirole	-11	± 10.5	< 0.0001

Negative values indicate improvement

Advanced Parkinson Disease

Poewe et al conducted a randomized, multicenter, double-blind, double-dummy placebo controlled and comparator controlled three arm parallel group study to determine the efficacy and safety of adjunct treatment with transdermal rotigotine in comparison with placebo and with pramipexole in patients with advanced Parkinson disease who were already being treated with levodopa.¹¹ A total of 506 patients were randomly assigned to receive rotigotine (n=204), pramipexole (n=201), or placebo (n=101). The study was conducted in 77 centers in Europe, South Africa, Australia, and New Zealand. In order to be eligible for the study, patients had to be 30 years or older (and not older than 80 years for sites in South Africa) and have been diagnosed with idiopathic Parkinson disease (as defined by the UK Brain Bank criteria) for more than three years. Patients had to have stable levodopa treatment regimens of at least 300 mg/day in three or more divided doses, with no change in dose within four weeks of study enrollment. Likewise, patients had to be on stable doses of any additional antiparkinsonian medication for at least four weeks prior to enrollment. Patients were included if they experienced motor fluctuations of the wearing-off type with an average of at least 2.5 hours per day spent in the “off” state, as self-assessed in home diaries. Patients also had to be assessed at Hoehn

and Yahr stage 2 or less when “on” and could not be worse than stage 4 when “off.”

Patients were excluded from the study for the following reasons: incomplete self-assessment diaries; if additional treatment with any dopamine agonist was required during the 4 weeks prior to self-assessment diary completion; suspicion of atypical parkinsonism; a history of previous surgery for Parkinson disease; Mini-Mental State Examination score <25; simultaneous hallucination or psychosis; history of orthostatic hypotension in the six months prior to enrollment; history of myocardial infarction in the 12 months preceding study enrollment; QTc interval >450 ms (men) or >470 ms (women); history of skin hypersensitivity to adhesives or other transdermal products; if patients had taken an investigational drug within four weeks of the pretreatment visit; or if concomitant treatment with dopamine agonists, monoamine oxidase A inhibitors, dopamine-releasing drugs, tolcapone, neuroleptics, cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, or quinine was necessary.

Following a screening phase of up to four weeks, during which inclusion and exclusion criteria were verified and the self-assessment diaries were completed, participants were randomly assigned to one of three treatment groups in a 2:2:1 ratio. Patient demographics and baseline characteristics were similar between all three treatment groups. Rotigotine was administered once-daily utilizing a transdermal patch. Patients were started on a 4 mg/24 hours dose which was increased by 2 mg/24 hours weekly, up to a dose that represented optimal patient response or a maximum dose of 16 mg/24 hours. Pramipexole was started at a dose of 0.375 mg/day for one week, and then increased to 0.75 mg/day. Patients had weekly dose adjustment thereafter of 0.75 mg/day in weekly increments up to a maximum of 4.5 mg/day in three divided doses. Investigators allowed patients to back-titrate their study medication doses during the titration phase. Those patients that required back titration immediately started the maintenance phase after their dose was reduced. Antiparkinsonian medications that patients were on at baseline were kept unchanged for the duration of the study except for total daily levodopa doses. The total daily levodopa dose could be reduced for dyskinesia development or worsening of existing dyskinesias during the first two weeks of the study’s maintenance phase. If the levodopa dose was reduced, patients were allowed to be re-titrated to the original baseline dose. In all other cases, the total daily levodopa dose had to remain stable for the duration of the study.

After an initial titration period of up to seven weeks during which study drug doses were titrated to efficacy and patient tolerability, study participants transitioned into a 16-week maintenance phase on stable study drug doses. Patients were then titrated off active treatment and a four week safety follow up period ensued.

The two primary efficacy endpoints were the change from baseline to end of the maintenance phase in absolute time spent “off”, as assessed by patient diaries, and the proportion of responders to treatment. Patients with 30% or more reduction in absolute “off” time from baseline to end of maintenance were defined as responders. Secondary endpoints included changes observed from baseline to the end of the maintenance phase for the following parameters: absolute time spent “on” without

troublesome dyskinesia; number of “off” periods; motor status after waking in the morning; and UPDRS II and III scores during “on” periods. Also assessed was the change in total levodopa dose, change in the duration of sleep each night, and other sleep disturbances as assessed with the Parkinson Disease sleep scale. Safety was assessed with documentation of adverse events, monitoring of vitals signs, lab parameters, daytime somnolence, and with physical and neurological examinations.

At the end of maintenance in the intent to treat population, the mean change in daily “off” time from baseline compared with placebo was -1.58 hours ($p < 0.0001$; 95% CI -2.27 to -0.90) for rotigotine and -1.94 hours ($p < 0.0001$; 95% CI -2.63 to -1.25) for pramipexole. Sixty-seven percent of patients treated with pramipexole were classified as responders, as compared to 59.7% of rotigotine-treated patients and 35% of patients in the placebo group.

An evaluation of secondary endpoints revealed that both study drugs were similar in efficacy and both were determined to be better than placebo for all secondary efficacy measurements. There was an increase in the absolute time spent “on” in the active treatment groups without troublesome dyskinesia. UPDRS scores improved similarly in the active treatment groups and were significantly improved over those in the placebo group ($p < 0.001$). Rotigotine was not inferior to pramipexole for the change in “off” time versus baseline.

Overall, the study had a 95% completion rate, with 15% of pramipexole patients, 11% of rotigotine patients, and 26% of placebo-treated patients withdrawing from the study. Study withdrawals were most commonly secondary to adverse effects. About 50% of the patients were on concomitant anti-parkinsonian medication, in addition to levodopa.

Most adverse reactions experienced were assessed to be mild to moderate in severity. Patients from all three treatment groups experienced adverse reactions with significant frequency; 66% of patients in the placebo group and 69% of patients in both the rotigotine- and pramipexole-treated groups experienced at least one adverse effect during the clinical trial. The most common adverse reactions reported in the rotigotine-treated patients included application site reactions and nausea. Dyskinesia, dizziness, and hallucinations were most commonly reported in the pramipexole group.

Several studies have reviewed the utility of rotigotine as a treatment for restless legs syndrome (RLS).^{12,13,14} These studies suggest that the continuous delivery of rotigotine by means of a patch may provide an effective treatment of RLS symptoms both during the night and day. These studies cite advantages over existing dopamine agonists including once-daily administration, absence of food interactions, maintenance of stable plasma levels and utility in patients with swallowing difficulties.

ADVERSE EFFECTS

Investigators evaluated adverse events for rotigotine in all three placebo-controlled studies in early-stage Parkinson disease.¹ Patients did not receive concomitant levodopa in these studies. Table 7 includes a summary of those adverse events that occurred in $\geq 2\%$ of patients treated with rotigotine and occurred more frequently than in the placebo group.

Some adverse events appear to be dose related, based on adverse event data collected from dose-ranging studies.¹ Certain adverse events (anorexia; constipation; abnormal vision) were found to be dose-related only when their onset was in the titration period. Dizziness was only dose-related when it had its onset in the maintenance period. Table 8 lists those adverse events noted to be dose-related.

DRUG INTERACTIONS

Based on drug characteristics and clinical experience to date, rotigotine has no clinically meaningful pharmacokinetic drug interactions.¹ Rotigotine was evaluated in combination with warfarin, cimetidine, digoxin, and levodopa and did not alter the kinetics of any of the medications. Rotigotine, the 5-O-glucuronide and its desalkyl and monohydroxy metabolites were analyzed for interactions with the human CYP isoenzymes. Based on these results, no risk for inhibition of CYP1A2, CYP2C9, and CYP3A4 catalyzed metabolism of other drugs is predicted at therapeutic rotigotine concentrations. There is a low risk of inhibition of CYP2C19 and CYP2D6 catalyzed metabolism of other drugs at therapeutic concentrations. It is possible that dopamine antagonists, such as antipsychotics or metoclopramide, could diminish the effectiveness of rotigotine. Patients should not drink alcohol or take other CNS depressants while using rotigotine.

TABLE 7. ADVERSE REACTIONS

Adverse Event	Rotigotine (n=649) (%)	Placebo (n=289) (%)
Nausea	38	15
Application site reactions	37	14
Somnolence	25	16
Dizziness	18	11
Headache	14	10
Vomiting	13	2
Insomnia	10	5
Fatigue	8	7
Extremity edema	7	6
Back pain	6	5
Accident (not otherwise specified)	5	4
Constipation	5	4
Increase sweating	4	2
Dyspepsia	4	1
Arthralgia	4	3
Dry mouth	3	1
Hypertension	3	2
Vertigo	3	2
Anorexia	3	1
Abnormal dreams	3	<1
Sinusitis	3	2
Urinary tract infection	3	1
Abnormal vision	3	1
Hallucination	2	1
Erythematous rash	2	1

TABLE 8. DOSE-RELATED ADVERSE REACTIONS

Adverse Event	Placebo (n=64) (%)	Daily Rotigotine Dose			
		2 mg/24 h (n=67) (%)	4 mg/24 h (n=63) (%)	6 mg/24 h (n=65) (%)	8 mg/24 h (n=70) (%)
Nausea	11	34	38	48	41
Application site reaction	19	24	21	34	46
Vomiting	3	10	16	20	11
Somnolence	3	13	16	19	21
Insomnia	8	6	13	14	14
Weight decrease	0	0	0	2	3
Myalgia	0	0	2	2	3
Abnormal dreams	0	2	5	3	7
Hallucination	2	0	2	3	3
Erythematous rash	2	2	6	3	3

MEDICATION SAFETY

Similarity between the brand name of rotigotine (Neupro) and the brand name of filgrastim (Neupogen) could result in errors in prescribing and computer order entry. Fortunately, the dosage forms are distinctly different as are the doses, so errors should be minimal.

Patients will need adequate instruction on application and patch removal techniques. The patch should be applied to clean, dry, and intact skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. The application site needs to be moved on a daily basis. Attempts should be made to avoid application to the same site more often than once every two weeks. If it becomes necessary to apply the rotigotine patch to hairy skin, the skin must be shaved at least three days prior to patch application.¹

Patients will need to be warned about the potential for sedation and the danger of falling asleep while they are engaged in activities of daily living, including the operation of motor vehicles, which has resulted in accidents.¹ Patients should be continually assessed for symptoms of drowsiness or sleepiness as these events can occur well after the start of treatment. There is currently not enough evidence to establish whether a dose reduction will eliminate occurrences of falling asleep during activities of daily living.

The backing layer of the rotigotine transdermal patch contains

aluminum.¹ This layer could lead to skin burns during procedures such as magnetic resonance imaging or cardioversion. Due to this fact, the rotigotine transdermal system should be removed prior to performing these procedures.

The effect that the application of heat might have on the rotigotine transdermal system has not been studied.¹ However, it is important to note that the exposure to heat with the use of other transdermal delivery systems has been shown to increase absorption of drug. Patients should be advised to avoid exposure to direct or indirect heat sources while using the rotigotine transdermal system including heating pads, electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

COST, DOSE AND HOW SUPPLIED

Rotigotine is available in cartons of seven and 30 transdermal systems in two strengths: 2 mg/24 hours and 4 mg/24 hours, and in a carton of 30 transdermal systems in the 6 mg/24 hours strength. The average wholesale price (AWP) of each strength and package size is outlined in Table 9. In comparison to other dopamine agonists, the AWP of rotigotine therapy is similar to that of bromocriptine, pramipexole and ropinirole as highlighted in Table 10.

TABLE 9. AVERAGE WHOLESALE PRICE (AWP) OF AVAILABLE ROTIGOTINE TRANSDERMAL SYSTEMS

Dose per 24 hours	System size (cm ²)	Rotigotine content	Package size	AWP
2 mg/24 hours	10	4.5 mg	7 or 30	\$19.69/\$84.38
4 mg/24 hours	20	9 mg	7 or 30	\$67.38/\$288.75
6 mg/24 hours	30	13.5 mg	30	\$288.75

TABLE 10. AVERAGE WHOLESALE PRICE (AWP) OF AVAILABLE SELECTED DOPAMINE AGONISTS

Agent	Initial dosing [Usual dosing]	Monthly AWP of initial dose [Monthly AWP of usual dose]
Pramipexole (Mirapex®)	0.125 mg three times daily [0.5 - 1.5 mg three times daily]	\$167.40 [\$232.20, flat price for higher dose strengths]
Ropinirole (Requip®)	0.25 mg three times daily [3 - 8 mg three times daily]	\$231.30 [\$246.60 - \$493.20]
Bromocriptine (Parlodel®)	1.25 mg twice daily [2.5 - 40 mg/day]	\$129.90 [\$129.90 - \$1,586.40]

CONCLUSION

Rotigotine is a novel new agent for the treatment of early-stage Parkinson disease and, while the clinical trials had strict exclusion criteria, the drug appears to offer a promising treatment option for patients suffering with the disease. There are limited published data evaluating rotigotine due to its recent development and approval. Three studies demonstrate the improvement in UPDRS scores for those patients using the rotigotine transdermal product for the treatment of early-stage Parkinson disease, while another study showed a similar achievement in "off" time for rotigotine and pramipexole in patients with advanced Parkinson disease. Rotigotine does offer an advantage over other dopamine agonists in that the transdermal delivery system avoids pulsatile dosing, which is hypothesized to cause dyskinesias and fluctuations in motor function. ●

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Present a Poster at the Educational Conference

PSW is currently accepting poster abstracts for the 2008 Educational Conference. Through posters, pharmacy practitioners can share unique practice ideas, programs or experiences with colleagues. The Poster Presentation Session is scheduled for Tuesday, April 22 from 4:30 p.m. to 7:00 p.m. concurrently with the Industry Forum and Reception. Poster topics may cover any area of pharmacy practice. Submissions by pharmacists, residents, students and pharmacy technicians will be considered. Posters will be chosen and accepted for presentation after review of a presenter's abstract submission. The deadline for submission is March 24, 2008. Abstract forms will be available on the PSW website or by contacting Sarah Boyce at the PSW office by phone or Email (sarahb@pswi.org).

Worth a Second Look

by Jennifer M. Goings, PharmD candidate
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Medication errors inevitably find their way into pharmacies on a daily basis. While the majority of these are caught, some are not. Preventing these errors from leaving the pharmacy is a top priority for supervisors and staff alike as they assess current quality control programs. Understanding where errors occur and how pharmacists can intervene in this process is vital.

Errors can occur at each stage of the prescription process: entry, filling, verification, and point of delivery. Point of delivery is one aspect that deserves additional attention, as this is the last opportunity for an error to be caught and prevented from leaving the pharmacy. Some medication errors have been classified in order to be used as a tool to identify the types of errors that transpire throughout the prescription process. The 2007 Pharmacists Mutual Claims Study found that 50 percent of claims involved the patient receiving the wrong drug, a category which included the delivery of a medication to an unintended party.

Several types of delivery errors exist: multiple patients' prescriptions may be bagged up together or a patient may leave with another's prescription. Retrieving items from the refrigerator yields yet another opportunity to erroneously dispense medication. Grabbing the incorrect insulin, drop, or suspension is easy to do if the pharmacy staff member fails to double check the product and patient name with the cash register receipt.

There are several easy steps that can be implemented into training to avoid these errors at delivery. Train all staff members to ask, "I have four prescriptions for you today, is that what you were expecting?" If there is a discrepancy between what is ready for the patient and what is expected, read the names of the prepared prescriptions to them. While the staff member is ringing up the receipts, they should also be checking to make sure each receipt bears the same name and address. This offers another opportunity to catch errors before they reach the patient. This time can also be utilized to inform the patient of changes in drug manufacturer so they are aware of differences in size, shape, or color of their medication to avoid confusion later. Use of a basket system also decreases the chance that patients' prescriptions will end up mistakenly grouped together as the pharmacist bags up the prescriptions. If delivery still occurs to the wrong patient, request that the prescription be brought directly back to the pharmacy or offer to send someone out to retrieve the prescription immediately. Apologize to the patient for the inconvenience and thank them for their help and understanding. Finally, follow up with the other patient involved in the mix-up to ensure they received the correct medication if it has already been picked up.

The point of delivery grants a valuable last chance to the pharmacy staff to prevent errors from leaving the pharmacy. These quick and simple extra steps may help to prevent a seemingly innocent error from becoming a serious medical emergency. ●

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