Rotigotine (Neupro)

National Drug Monograph

March 2013

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

- Rotigotine is a dopamine agonist approved for use for the treatment of signs and symptoms of idiopathic Parkinson's disease (PD) in addition to moderate to severe restless legs syndrome (RLS).
- Rotigotine is the only dopamine agonist available in patch formulation and provides a steady blood level of drug over 24 hours.
- The most common side effects, occurring more frequently than placebo in Phase II and III clinical trials include application site reaction, somnolence, dizziness, nausea, and insomnia.
- Numerous reports of patients suddenly falling asleep, in the absence of significant somnolence, have been reported, several of which have occurred in patients operating motor vehicles. In a meta-analysis of patients taking low-dose rotigotine, 1-3mg/24 hours for RLS, 2% of the study population experienced such sleep attacks. In addition, published reports of patients exhibiting compulsive behaviors, such as urges to gamble or sexual urges, have been of concern.
- Rotigotine, is a safe, effective treatment for both early and advanced PD, and is another dopamine agonist option for select patients. Non-inferiority of rotigotine was not consistently demonstrated in primary efficacy measures compared to ropinirole and pramipexole in early and advanced PD, respectively.
- Rotigotine appears to have a similar efficacy and side effect profile as pramipexole and ropinirole at recommended doses, with the exception of application site reactions, which sometimes required drug discontinuation.
- For the treatment of RLS, two placebo-controlled trials have demonstrated the efficacy of rotigotine versus placebo. There are no active comparator trials available which document superiority over other dopamine agonists for RLS.
- In terms of general efficacy and safety, rotigotine does not appear to provide advantages over immediate release oral dopamine agonists, while being more expensive. However, rotigotine may be a reasonable therapeutic option for patients with difficulty swallowing or medication compliance issues (patient or caretaker) that could be addressed by use of the patch. In addition, it may be an option for patients with severe renal impairment (CrCl <30ml/min), pramipexole also has renal dosing for patients with very severe impairment (creatine Cl > 15mL/min and hemodialysis).

Introduction[1]

Rotigotine was originally approved by the FDA April 2007 but was removed from the market in 2008 due to drug crystal formation on the patch that led to decreased drug availability and altered efficacy. Rotigotine was originally refrigerated during storage but the FDA requested the manufacturer to develop an entirely new drug formulation. The new formulation was approved and came back to the US market in July 2012. The purposes of this monograph are to (1) evaluate the safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating rotigotine for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[2-4]

The exact mechanism of rotigotine in the treatment of Parkinson's disease and Restless Legs Syndrome is unknown, but believed to be due to the drug's dopaminergic properties. Rotigotine is a non-ergoline dopamine agonist that stimulates dopamine receptors in the caudate-putamen in the brain. Rotigotine primarily binds D2 receptors, and acts to a lesser extent on D3 and D1 receptors.

Rotigotine is absorbed via a transdermal system, with an approximate 3 hour lag time from when the patch is initially applied and when the drug is detected in plasma. Clinical studies showed steady-state plasma concentrations were achieved within 2 to 3 days of initiation. At this time there are no recommendations as to initiating therapy with an oral load of an alternative dopamine agonist. T_{max} occurs between 15 to 18 hours post-dose on average, with the peak concentration being dose-related. Terminal half-life of the drug is 5 to 7 hours. Rotigotine is 89.5% bound to human plasma proteins in vivo. Bioavailability for the different application sites at steady-state was measured, showing differences of as low as 1% (abdomen vs. hip) to as high as 46% (shoulder vs. thigh). Despite these measured differences in bioavailability between application sites, overall mean plasma concentrations were stable over the six months of evaluation, and patients are encouraged to utilize all of the previously mentioned application sites.

Rotigotine is metabolized by conjugation and N-dealkylation, catalyzed by multiple CYP enzymes, sulfotransferases and two UDP-glucuronosyltransferases. Approximately 71% is excreted in urine, 23% is excreted in feces, and 11% is renally eliminated. Less than 1% of the absorbed dose is renally eliminated as unconjugated drug.

FDA Approved Indications[2-4]

Rotigotine is approved by the FDA for the treatment of signs and symptoms of idiopathic Parkinson's disease. Efficacy of rotigotine was demonstrated in controlled trials in both early-stage Parkinson's disease patients not receiving concomitant levodopa in addition to advanced-stage Parkinson' patients that were treated with concomitant levodopa. Rotigotine is also FDA approved for the treatment of moderate to severe primary Restless Legs Syndrome.

Potential Off-label Uses[5]

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Case studies have suggested rotigotine may have potential for benefit in patients with Aromatic L-Amino Acid Decarboxylase Deficiency.

Current VA National Formulary Alternatives[2-4,6-7]

Alternative dopaminergic agents include levodopa (carbidopa/levodopa), bromocriptine, pramipexole, and ropinirole. Levodopa is the precursor to dopamine and is metabolized to dopamine in the central nervous system. Bromocriptine is an ergoline compound dopamine agonist, derived from ergot alkaloids, whereas pramipexole and ropinirole are non-ergoline dopamine agonists. Carbidopa/levodopa and ropinirole are available on the national formulary while bromocriptine and pramipexole are available through the non-formulary process. Apomorphine, an injectable dopamine agonist indicated for rescue use in patients with intractable "off" periods, is on formulary, restricted in VA to use by neurology providers.

Agents for the treatment of Restless Legs Syndrome included on the National Formulary include ropinirole, bromocriptine, levodopa, clonazepam, diazepam, gabapentin, tramadol, codeine, oxycodone, hydrocodone, methadone, and zolpidem. Non-formulary agents include pramipexole, triazolam, and zaleplon.

Dosage and Administration[2-3,8]

Rotigotine is available as a transdermal system (patch) in 1mg, 2mg, 3mg, 4mg, 6mg and 8mg of rotigotine per 24 hours. A single or multiple patches may be applied to achieve the appropriate dosage. The patch is to be applied once daily, at approximately the same time each day. Because rotigotine is delivered via transdermal system, food is not likely to affect absorption of the drug and patients may choose an application independently of meal times. See the below "application instructions" and "removal instructions" for further guidance on proper patch administration. In the event that the patch becomes dislodged, another patch should be applied for the remainder of the 24 hour dosing period.

No dosage adjustment is required in patients with any degree of renal impairment, including patients on dialysis, or moderate hepatic impairment (Child-Pugh classification grade B). No information is available for patients with severe hepatic impairment.

Early-Stage Parkinson's Disease: Start at 2mg/24 hours and increase by 2mg/24 hours every week based on individual patient response and tolerability. In clinical trials, 4mg/24 hours was the lowest effective dose and a dose of 6mg/24 hours is not to be exceeded in patients with early-stage Parkinson's disease.

Advanced-Stage Parkinson's Disease: Initiate rotigotine at 4mg/24 hours and increase by 2mg/24 hours every week based on individual patient response and tolerability. The recommended dose for this indication is 8mg/24 hours.

Restless Legs Syndrome: Initiate rotigotine at 1mg/24 hours and increase by 1mg/24 hours every week based on individual patient response and tolerability. In clinical trials, the lowest effective dose was 1mg/24 hours and the highest recommended dose is 3mg/24 hours.

Discontinuation: Dose changes and withdrawal of dopamine agonists can precipitate neuroleptic malignant syndrome-like reactions and dose tapering is recommended for discontinuation. For patients with Parkinson's disease, the dose should be reduced by no more than 2mg/24 hours, reducing the dose every other day until complete withdrawal is achieved. For patients with Restless Legs Syndrome, reduce the dose by 1mg/24 hours every other day until complete withdrawal is achieved.

Application instructions: The patch is to be applied once daily at approximately the same time each day at any time that is convenient to the patient. Apply the patch to clean, dry, intact skin of the hip, flank, shoulder, upper arm, thigh, or abdomen. Do not apply patch to skin that is irritated, oily, or damaged. In addition, avoid areas that will be rubbed by tight clothing such as waistbands. The application site is to be rotated daily, and any one application site should not be used more than once in 14 days. If the patch must be applied to an area with hair, shave the area at least 3 days prior to application. To apply the patch, first pull the two sides of the protective pouch apart. Next remove the patch from the pouch and bend both edges of the patch away from the S-shaped cut in the center of the protective film covering the pouch. Peel off one-half of the protective film and apply the sticky portion to the skin. Avoiding touching the medication on the patch, remove the remaining half of the film and hold the palm of your hand firmly over the patch for 30 seconds. Remember to wash your hands after application to remove any medication that may have transferred to your hands.

Patch removal: slowly peel the patch off of the skin. Fold the patch in half so that the sticky sides are folded together. Throw away the patch in a trashcan that is inaccessible by children or pets. Wash the area of skin with warm, soapy water to remove any residue or adhesive that remains on the skin.

Switching from oral dopamine agonists to rotigotine: An open-label study of 99 subjects with Parkinson's disease was conducted in which the subjects, previously treated with 3 to 12mg/day ropinirole with or without levodopa, were converted to treatment with transdermal rotigotine. The following dosage conversion was utilized; 3mg/day ropinirole to 2mg/24 hours rotigotine, 6mg/day ropinirole to 4mg/24 hours rotigotine, 8-9mg/day ropinirole to 6mg/24 hours rotigotine, 12mg/day ropinirole to 8mg/24 hours rotigotine. Patients were instructed to take their last dose of ropinirole in the afternoon or evening, applying a rotigotine patch the next morning upon awakening. Overall this study determined that an overnight switch from ropinirole to rotigotine was generally well tolerated without loss of efficacy. Generalization of these findings for converting from other dopamine agonists was not discussed.

Efficacy[9-15]

Efficacy Measures

The Unified Parkinson's Disease Rating Scale (UPDRS) is a rating tool designed to follow the longitudinal course of Parkinson's disease and assess response to therapy. Many neurologists find it too cumbersome to use in clinic, however it can help determine when patients' symptoms are problematic enough to require pharmacologic treatment. Treatment with either levodopa or the dopamine antagonists can result in improvement on the UPDRS score. The entire scale can be viewed http://neurosurgery.mgh.harvard.edu/functional/pdstages.htm and has been in use since 1987. A total of 199 points are possible with 0 representing no disability and 199 representing total disability. The scale is divided into six sections as follows:

I. Mentation, Behavior and Mood
II. Activities of daily living (ADLs) taking both "on" and "off" symptoms into account
III. Motor Examination
IV. Complications of Therapy (in the past week); Complications are divided into:
    a. Dyskinesias,
    b. Clinical fluctuations
    c. Other complications
V. Modified Hoehn and Yahr Staging

VI. Schwab and England Activities of Daily Living Scale

Both the Modified Hoehn and Yahr Staging scale and the Schwab and England Activities of Daily Living Scale, parts V and VI of the UPDRS rating tool, were in use prior to introduction of the UPDRS tool and have been incorporated into the scale.

Summary of Efficacy Findings

Early-Stage Parkinson's Disease: Two Phase III studies examined the efficacy of transdermal rotigotine in patients with early-stage Parkinson's disease. Watts, et al evaluated the drug's efficacy compared to placebo, finding that rotigotine significantly improved motor function and activities of daily living (evaluated as UPDRS II+III score) as compared to placebo. Giladi, et al compared rotigotine to both placebo and ropinirole, showing significantly improved responder rates and improvement in UPDRS II+III scores compared to placebo. However, rotigotine did not show non-inferiority to ropinirole for the primary efficacy measure and the study was not powered to show superiority.

Advanced Parkinson's Disease: LeWitt, et al in the PREFER study examined the efficacy of rotigotine versus placebo in patients with suboptimal control of Parkinson's symptoms and significant motor complications, defined as "off" times of >2.5 hours per day. Rotigotine exhibited statistically significant reduction in absolute "off" time, in addition to increases in daily "on" time without troublesome dyskinesias, as compared to placebo. In addition, Poewe, et al examined the efficacy of rotigotine, as compared to placebo and pramipexole, in the CLEOPATRA-PD trial. Rotigotine was determined to be superior to placebo and non-inferior to pramipexole in absolute reduction in "off" time per day. Both trials also showed significantly higher proportions of patients with >30% improvements in "on" time compared to placebo.

Restless Legs Syndrome: Restless Legs Syndrome: Hening, et al and Trenkwalder, et al evaluated efficacy of rotigotine in RLS patients in two separate phase III clinical trials. Both studies resulted in a significant change in IRLS and CGI (RLS disease severity scales) with rotigotine 1-3mg/24 hours as compared to placebo.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 13).

Adverse Events (Safety Data)[2,5-15]

The adverse event profile of rotigotine mirrors those of other dopamine agonist. The most commonly occurring adverse events in clinical trials were application site reaction, vomiting, somnolence, dizziness, fatigue, and headache. Most adverse events were mild to moderate; however significant numbers of rotigotine-treated patients discontinued treatment due to adverse events, most commonly application site erythema and pruritus, which resolved upon discontinuation of the drug.

Adverse events in early-stage Parkinson's patients in which incidence in rotigotine was ≥5% higher than incidence in placebo patients.

Adverse Reaction	Placebo N=64 %	Rotigotine dose			
		2mg/24h N=67 %	4mg/24h N=64 %	6mg/24h N=65 %	8mg/24h N=70 %
Nausea	13	34	38	48	41

Vomiting	3	10	16	20	11
Somnolence	3	12	14	19	20
Application site reaction	19	24	21	34	46
Dizziness	11	21	14	22	20
Anorexia	0	0	2	6	4
Hyperhidrosis	3	3	3	11	3
Insomnia	6	5	10	11	7
Fatigue	3	8	18	6	13
Abnormal Dreams	0	2	5	3	7
Depression	0	5	3	2	0

Portions of this table adapted from Neupro (rotigotine) package insert

Adverse events in Advanced Parkinson's patients in which incidence in rotigotine was ≥5% higher than incidence in placebo patients.

	Placebo N=120 %	**Rotigotine 8mg/24h N=118 %**
Application site reaction	13	36
Nausea	19	28
Somnolence	28	32
Headache	5	10
Dyskinesia	7	14
Peripheral Edema	1	9

Portions of this table adapted from Neupro (rotigotine) package insert

Adverse events in Restless Legs Syndrome patients in which incidence in rotigotine was ≥5% higher than incidence in placebo patients.

	Placebo N=217 %	**Rotigotine Dose**		
		1mg/24h N=215 %	**2mg/24h N=211 %**	**1mg/24h N=220 %**
Application site reaction	4	27	38	43
Nausea	10	15	23	21
Somnolence	4	5	8	10

Headache	11	15	18	16
Disturbance in initiating/ Maintaining sleep	3	4	3	10
Muscle Spasms	1	1	4	1

Portions of this table adapted from Neupro (rotigotine) package insert

Tolerability

The following are the rates of discontinuation of rotigotine in clinical trials due to adverse events, as compared to placebo.

Early Parkinson's :	12% (rotigotine 6mg/24 hours) vs. 6% placebo
Advanced Parkinson's:	15% (rotigotine 8mg/24 hours) vs. 9% placebo
Restless Legs Syndrome:	24% (rotigotine 3mg/24 hours) vs. 3% placebo

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 13).

Contraindications[2-4]

Rotigotine is contraindicated in patients who are hypersensitive to rotigotine or any component of the transdermal delivery system.

Warnings and Precautions[2-4,11,13]

Sulfite Sensitivity: Rotigotine contains sodium metabisulfite, a chemical most frequently used as a preservative to prevent discoloration in food and wine. Patients with sulfite sensitivity may experience allergic reactions, including anaphylaxis or asthmatic episodes.

Falling Asleep During Activities of Daily Living / Somnolence: Instances of patients treated with rotigotine falling asleep while engaged in activities of daily living, including operating a motor vehicle, have been reported. In addition, some patients that experienced these events reported feeling alert just prior to the event and having no warning signs of excessive somnolence. In addition, there is no temporal relationship between the initiation of rotigotine and the occurrence of somnolence, as reports of such events have been made up to one year after initiation of the drug.

Hallucinations / Psychotic-like Behavior: Patients with advanced-stage Parkinson's disease were at an increased risk of hallucinations, with the incidence increasing with escalating doses. Post-marketing reports have shown an increase of new or worsening mental status and behavioral changes, most of which presented during initiation or dose escalation. The various manifestations of mental status and behavioral changes include: aggressive behavior, agitation, psychotic-like behavior, confusion, hallucinations, delusions, disorientation, and delirium. Patients with a major psychotic disorder should not use rotigotine due to the potential for exacerbation of psychosis.

Symptomatic Hypotension: Patients are at an increased risk for significant decreases in blood pressure or orthostatic hypotension, especially during the period of dose escalation. The mechanism of orthostatic hypotension is believed to be due to the impairment of systemic regulation of blood pressure by dopaminergic agonists. In addition, patients with Parkinson's disease tend to have impaired capacity for blood pressure response to postural changes.

Syncope: Syncopal episodes have been reported in patients using dopamine agonists such as rotigotine. Use caution in patients with cardiovascular disease.

Impulse Control / Compulsive Behaviors: Case reports in patients treated with one or more medications that increase central dopaminergic tone, including rotigotine, have shown impaired impulse control, including the following behaviors: sexual urges, urges to gamble, binge eating, urges to spend money.

Elevation of Blood Pressure / Elevation of Heart Rate: Some patients treated with rotigotine experienced moderate to severe increases in systolic blood pressure, defined as >180 mmHg, and/or increases in diastolic blood pressure, defined as >105 mmHg while supine/standing. Others experienced mild to moderate increases in supine blood pressure, defined as systolic pressure $\geq$120 mmHg and/or diastolic pressure $\geq$10 mmHg. Some patients exhibited pulses >100 beats per minute while supine/standing.

Weight Gain / Fluid Retention: Patients treated with rotigotine have increased incidence of weight gain as compared to placebo. Weight gain usually manifests as peripheral edema, indicating the rotigotine causes some degree of fluid retention. Caution should be used in patients with congestive heart failure or renal impairment, as they may be vulnerable to negative outcomes with fluid retention.

Dyskinesia: Because of its dopaminergic properties, rotigotine may potentiate the dopaminergic side effects associated with levodopa therapy. In addition, rotigotine may exacerbate pre-existing dyskinesia.

Application Site Reactions: Application site reactions to the rotigotine transdermal system exhibit a dose-dependent relationship. Most reactions were mild to moderate in severity and include symptoms such as edema, pruritus, and erythema. Rotigotine should be discontinued if a generalized skin reaction is observed.

Melanoma: In general, patients with Parkinson's disease have exhibited increased risk of melanoma when compared to the general population. A causal relationship to drugs used to treat Parkinson's disease has not been established.

Augmentation and Rebound in RLS: Dopaminergic medications may lead to augmentation of RLS symptoms. Rebound, an end of dose effect, may be experienced when a rotigotine dose wears off or the medication is discontinued.

Magnetic Resonance Imaging / Cardioversion: Rotigotine transdermal system should be removed prior to magnetic resonance imaging or cardioversion, as the backing layer contains aluminum and may lead to skin burns.

Heat Application: The application of heat to various transdermal deliver systems has shown to increase the absorption. Patients should avoid heat sources such as heating blankets, saunas, prolonged sun exposure, and heat lamps.

Withdrawal-Emergent-Hyperpyrexia / Confusion: Rapid dose reduction, withdrawal, or changes in anti-parkinsonian therapy have been reported to cause a complex of symptoms including muscular rigidity, elevated body temperature, rhabdomyolysis, and autonomic instability (resembling neuroleptic malignant syndrome). It is advised to taper the dose of rotigotine at the end of treatment, as a prophylactic measure to avoid this syndrome.

Fibrotic Complications: Cases of the following fibrotic complications have been reported with ergot-derived dopaminergic agents: pleural effusion, pulmonary infiltrates, retroperitoneal fibrosis, pericarditis, and cardiac valvulopathy. As rotigotine is a non-ergoline agent, the potential for these complications is unknown.

Binding to Melanin: Clinical trials in rats and monkeys exhibited binding to melanin-containing tissues after a single dose of rotigotine, which slowly cleared over a 14 day period. This same finding has been reported with other dopamine agonists.

Special Populations[2-4]

Pregnancy: Pregnancy category C. There are no well controlled studies in pregnant women, but studies in mice, rats, and rabbits showed adverse effects on embryo-fetal development when the drug was given in doses lower than clinically indicated. Risk vs. benefit should be evaluated prior to using rotigotine in pregnant women.

Lactation: Rotigotine was shown to be excreted in rat milk, but it is unknown as to whether the drug is excreted in human milk. Rotigotine decreased prolactin levels and therefore may inhibit lactation.

Pediatric Use: No information available

Geriatric Use: Although greater sensitivity of elderly patients cannot be ruled out, no differences in safety, efficacy, or response have been observed among patients of varying age. Skin changes with advanced age may lead to increased drug exposure.

Renal Impairment: Renal function has been shown to have no clinically significant effect on rotigotine plasma concentrations.

Hepatic Impairment: Moderate hepatic impairment (Child-Pugh classification Grade B) has shown no clinically significant effect on rotigotine plasma concentrations. No guidance is available for patients with severe hepatic impairment.

Sentinel Events[2-4,11,13]

Case reports of patients experiencing sudden onset of sleep have surfaced through the course of Phase II and Phase III clinical trials with rotigotine. In one study of 242 subjects, one subject experienced suddenly falling asleep while driving a motor vehicle and another subject reported a brief loss of consciousness while driving. A post-hoc analysis of patients taking low dose rotigotine 1-3mg/24 hours for RLS established that 4 patients (2% of the sample) experienced a sleep attack or sudden onset of sleep.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LA/SA for generic name rotigotine: rasagiline, rivastigmine, ropinirole

LA/SA for trade name Neupro: Neupogen®, Neurontin®

Drug Interactions[2-4]

Drug-Drug Interactions
Rotigotine is metabolized by a variety of pathways, making inhibition of any one pathway unlikely to significantly alter rotigotine metabolism.

Anti-psychotics: concomitant administration of dopamine antagonists, such as antipsychotics, could diminish the effectiveness of rotigotine as their mechanisms of action are likely to counteract one another.

Anti-emetics: concomitant use of rotigotine and anti-emetics with dopamine antagonist properties may cause a worsening in rotigotine efficacy.

- Prochlorperazine
- Promethazine
- Droperidol
- Theithylperazine

L-dopa: Concomitant use of rotigotine with L-dopa may cause worsening of pre-existing dyskinesias. L-dopa 100mg/carbidopa 25mg twice daily with rotigotine 4mg/24 hours had no effect on the pharmacokinetic profile of either agent.

CNS Depressing Agents: Concurrent use of rotigotine with agents that cause CNS depression can potentiate sedative effects of rotigotine.

Dopamine agonists: Concomitant administration of rotigotine with dopaminergic agents, including memantine, may enhance the pharmacologic effect and kinetic profile of either agent. Dose reductions may be required.

Drug-Lab Interactions
Decreases below the normal reference ranges occurred for the following lab tests: hemoglobin, hematocrit, serum ferritin, and glucose. Increases above normal reference range occurred for serum BUN. T-wave abnormalities on EKG were detected in a small number of patients.

Acquisition Costs

Please refer to the last page for VA drug acquisition costs. Prices shown in this internal, draft document may include additional discounts available to VA. This information is considered strictly confidential and must not be shared outside of VA. All cost information will be removed from the document when posted to the PBM website.

Pharmacoeconomic Analysis[16-20]

A retrospective study of health insurance claims in the United States, between Jan 1, 1999 and Dec 321 2002, estimated the annual direct medical cost of PD at $10,349 per patient, with an additional $25,326 per patient in indirect costs. The total cost of Parkinson's disease in the United States, when accounting for direct and indirect cost, lost productivity and uncompensated caregivers, was estimated to be $23 billion annually. Additionally, RLS has been estimated to

increase annual healthcare expenditures by $4,464 per patient per year, with the main driver of this cost increase being from outpatient services ($2,405 increase annually).

Benhaddi and colleagues conducted a study to evaluate the cost effectiveness of rotigotine for treatment of early-stage PD in Scotland. The researchers performed a Markov state transition model, consisting of 5 "health states," corresponding to the 5 Hoehn and Yahr stages and one defined as "death." Because UPDRS scores are typically utilized as the primary endpoint in clinical trials, Hoehn and Yahr scores were translated into UPDRS scores. Patients began at the stage corresponding with their Hoehn and Yahr score, and transitioned through 3 month cycles. Ropinirole was chosen as the main comparator, as it is the standard dopamine agonist used for Parkinson's treatment. An algorithm to estimate a quality of life multiplier was utilized, taking into account UPDRS for ADLs and motor complications, in addition to comorbidities. Estimation of QALYs gained with treatment was determined by combining survival with the quality of life multiplier. Over a 5-year evaluation period, treatment with rotigotine resulted in an estimated 2.30 QALYs, compared to 2.26 for ropinirole. 10-year outcomes were 3.22 QALYs with rotigotine and 3.17 for ropinirole. Overall, rotigotine resulted in higher discounted QALYs (0.06), and a cost savings of £4642, as compared to ropinirole.

Aguirre and Benitez utilized a decision analytic model to evaluate the cost effectiveness of rotigotine in Mexico. Rotigotine was compared to pramipexole, the standard dopamine agonist used in this area. Rotigotine 4mg, 6mg, 8mg, and 12mg/24 hours doses were used (of note, 8mg/24hours is the maximum recommended dose for advanced-PD patients) compared to 3mg an 4.5mg/day doses of pramipexole. The analysis focused on the acquisition costs of study medication and costs associated with treating side effects related to the medications, such as lab tests, hospitalization, and physician charges. The average cost-effectiveness ratio for rotigotine 4mg, 6mg, and 8mg/24 hours ($923, $1,136, and $1,374) , in US dollar equivalents, were lower than for pramipexole 4.5mg/day ($1,585).

Conclusions

Rotigotine was compared to oral ropinirole in early PD (PD-3) and to pramipexole in advanced PD (CLEOPATRA). Each of the trials was designed and powered to demonstrate non-inferiority of rotigotine to active treatment in the primary efficacy measures. In PD-3, the difference between the rotigotine transdermal patch and ropinirole for the primary efficacy measure, proportion of responders with a $\geq$20% decrease in the UPDRS Parts II+III score, did not show non-inferiority. Exploratory post-hoc analyses comparing UPDRS Parts II+III score in 1)subgroups rotigotine <8mg/24 hours and ropinirole $\leq$12 mg/day and 2)comparable duration of the maintenance phase of 24 weeks, did not show statistically significant differences between the two treatments. Rotigotine and ropinirole had similar side effect profiles and occurrence, with the exception of more application site reactions with rotigotine. Lower frequencies of nausea, dizziness, and somnolence were observed with the rotigotine transdermal patch compared with ropinirole. In CLEOPATRA, rotigotine was non-inferior to pramipexole with regard to change in absolute off time. However, responder rates were somewhat greater in the pramipexole group than they were in the rotigotine group, and rotigotine was not shown to be non-inferior to pramipexole for this measure. Rotigotine and ropinirole were similar for other secondary measures, including absolute time spent on without troublesome dyskinesias, number of off periods, motor status after morning wake-up, UPDRS II and III scores, and sleep quality. The adverse event profiles of both active treatments in CLEOPATRA were similar, with small differences of more nausea with rotigotine and more reports of hallucinations, dyskinesias, and dizziness with pramipexole.

Two placebo-controlled trials demonstrated the efficacy of rotigotine in patients with RLS. The study conducted by Hening, et al (RLS-1), was designed and powered to demonstrate superiority of rotigotine to placebo. The difference between rotigotine and placebo for the primary efficacy measure, decrease from baseline to end of maintenance phase in IRLS sum score (symptom severity) and CGI item 1 score (level of "illness"), was statistically significant for both measures. The study by Trenkwalder, et al (RLS-2) examined the efficacy of rotigotine in patients with moderate-to-severe RLS. This study included both de novo patients, or those that had not previously been treated with a dopaminergic agent for RLS, and those who had previously received and shown a response to a dopaminergic agent. The difference in primary endpoints, decrease from baseline to end of maintenance phase in IRLS sum score (symptom severity) and CGI item 1 score (level of "illness"), were statistically significant between the rotigotine-treated groups and placebo. In addition, no difference was noted in response rates of de novo patients and those previously treated with dopaminergic agents.

Current VHA PBM-MAP Pharmacotherapy Recommendations in Parkinson's Disease list dopamine agonists as an initial option in 1)the early stages of disease in younger patients without cognitive impairment to attempt delay in the development of motor complications, 2)to prevent the development of peak dose dyskinesias by allowing reduction of the levodopa dose, and 3)to reduce "off" time in combination with levodopa therapy. Rotigotine, is a safe, effective treatment for both early and advanced PD, and is another dopamine agonist option for select patients. Non-inferiority of rotigotine was not consistently demonstrated in primary efficacy measures compared to ropinirole and pramipexole in early and advanced PD, respectively. Rotigotine appears to have a similar efficacy and side effect profile as pramipexole and ropinirole at recommended doses, with the exception of application site reactions, which sometimes required drug discontinuation. In terms of general efficacy and safety, rotigotine does not appear to provide advantages over immediate release oral dopamine agonists, while being more expensive. However, rotigotine may be a reasonable therapeutic option for patients with difficulty swallowing or medication compliance issues (patient or caretaker) that could be addressed by use of the patch. In addition, it may be an option for patients with severe renal impairment (CrCl <30ml/min). However, pramipexole also has renal dosing for patients with very severe impairment (creatine Cl > 15mL/min and hemodialysis).

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline using the search terms "rotigotine" and "Neupro." The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. Only randomized controlled trials published in peer-reviewed journals were included.

<table>
<tr><th>Trial</th><th>Inclusion/Exclusion</th><th>Endpoints</th><th>Results/ Study Assessment</th><th>ADRs/Tolerability</th></tr>
<tr>
<td>Watts, et al.[10]

Phase III, MC, R, DB, PC, PG, two-arm

<u>Treatments</u>
Rotigotine, started at 2mg/24 hours and titrated to max tolerable dose up to 6mg/24 hours, vs. placebo

Duration:
Titration: 3 weeks
Maintenance: 24 weeks
Safety follow-up: 4 weeks</td>
<td><u>Inclusion</u>
Age > 30 years, idiopathic PD diagnosis for ≤5 years, UPDRS motor score of ≥10 at baseline, Hoehn and Yahr stage 3 or less, MMSE score of ≥25, no other suspected cause of PD, and two or more of the following signs of PD: bradykinesia, resting tremor, rigidity, postural instability. Patients taking concomitant amantadine, MAOI, or anticholinergics if dose was stable 28 days prior to baseline and throughout the trial duration.

<u>Exclusion Criteria</u>
Prior or current dopamine agonist therapy, Carbidopa-Levodopa w/I 28 days prior to baseline visit or for ≥6 months, atypical PD, surgical intervention for PD, epilepsy, seizure history, stroke, TIA, or clinically relevant renal, hepatic, or cardiac dysfunctions.</td>
<td><u>Endpoints</u>
Primary:
Change in UPDRS II+III from baseline to end of maintenance phase

Secondary:
“responder” analysis – responder being defined as any subject with a change in UPDRS II+III of ≥20% from baseline to end of maintenance phase

Safety:
ADRs, vitals, body weight, ECG, lab values

<u>Concomitant medications at baseline</u>
Anticholinergics: 1.08 %
Amantadine: 13.7%
L-dopa: 0.7%
MAO-B inhibitor: 12.6%</td>
<td><u>Baseline:</u> No statistically significant differences between groups; average age of 63 years, 60% males in the placebo group and 68% males in the rotigotine group, mean 1.33 years since PD diagnosis.

Mean rotigotine dosage: 5.7 ± 0.84 mg/24 h
115 patients received a 6-mg/24 h dosage for the duration of the maintenance period

Endpoints
<table><tr><th></th><th>Placebo (n=96)</th><th>Rotigotine (n=181)</th><th>P-value 95% CI</th></tr><tr><td>Primary : Change in UPDRS II+III (±SD)</td><td>+1.31 (±0.956)</td><td>-3.98 (±0.707)</td><td><0.0001 (-7.6, 2.96)</td></tr><tr><td>Secondary: Responder analysis</td><td>19%</td><td>48%</td><td><0.0001 (0.18, 0.394)</td></tr></table>
Study Assessment:
• Intention-to-treat analysis
• Study primarily funded by Schwarz Pharma, maker of Neupro®
• Study defined and met power
• Primary endpoint was combination of motor and ADL scores, however these patients may be too early in PD disease course to see such drastic motor fluctuations
• 95% confidence interval crosses zero for the primary endpoint</td>
<td>Adverse Events:
<table><tr><th></th><th>Placebo, %</th><th>Rotigotine, %</th></tr><tr><td>ASR</td><td>12</td><td>44</td></tr><tr><td>Nausea</td><td>16</td><td>75</td></tr><tr><td>Somnolence</td><td>19</td><td>60</td></tr><tr><td>Dizziness</td><td>12</td><td>34</td></tr><tr><td>Headache</td><td>9</td><td>29</td></tr><tr><td>Insomnia</td><td>3</td><td>17</td></tr></table>
Discontinuation due to ADR:
<table><tr><th>Placebo</th><th>Rotigotine</th></tr><tr><td>6%</td><td>14%</td></tr></table></td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Inclusion/Exclusion</th><th>Endpoints</th><th>Results/ Study Assessment</th><th>ADRs/Tolerability</th></tr>
<tr>
<td>Giladi, et al.[11]

MC, R, DB, DD, Placebo and ropinirole controlled

<u>Treatments:</u>
Rotigotine 2, 4, 6, 8mg/24 hours vs. ropinirole with max dose of 24mg/day.

Duration:
Titration: rotigotine up to 4 weeks; ropinirole up to 13 weeks
Minimum dose-maintenance: ropinirole 24 weeks; rotigotine 33 weeks
Safety follow-up: 4 weeks</td>
<td><u>Inclusion</u>
age >30 years, PD diagnosis based on UK Brain Bank Criteria, mild to moderate disease defined as Hoehn and Yahr clinical stage of 3 or less, score of at least 10 on motor exam (part III) of UPDRS, permitted to take concomitant amantadine, selegiline, anticholinergics, or CNS active drugs if maintained at stable dosages for 28 days prior to baseline and for the duration of the trial.

<u>Exclusion Criteria</u>
MMSE score <25, clinically significant psychiatric or cognitive condition, inability to proper apply/remove patches, history of skin sensitivity to transdermal meds/adhesives, dopamine agonist or levodopa within 28 days of baseline, or ever taking levodopa for longer than 6 months, significant hepatic, renal, or cardiac dysfunction, prolonged QTc interval of <u>≥</u>450 ms for men or<u>≥</u>470 ms for women, symptomatic orthostatic hypotension, recent exposure to MAO-A or neuroleptics.</td>
<td><u>Endpoints</u>
Primary:
Proportion of “responders” to treatment, defined as patient with >20% decrease in the UPDRS parts II+III scores from baseline to end of maintenance period
Secondary:
(1) absolute change in UPDRS II+III scores from baseline to end of maintenance period, (2) change in UPDRS part II+III subscale scores, (3) demonstration of noninferiority to ropinirole
Post-hoc analysis:
(1) Analysis of those taking ropinorole <u><</u>12mg/day vs. those taking rotigotine up to 8mg/24 hours, (2) evaluation of first 24 weeks of maintenance therapy to compensate for unequal maintenance periods
Safety:
adverse events, changes in vital signs, body weight, ECG, laboratory values</td>
<td>92% of rotigotine patients reached the maximum dose of 8mg/24 hours
26% of ropinirole patients reached the maximum dose of 24mg/day
• Mean ropinirole dose was 14.1 mg/day

<table>
<tr><th></th><th>Placebo (n=118)</th><th>Rotigotine (n=215)</th><th>Ropinirole (n=228)</th><th>P-value</th></tr>
<tr><td>Primary: responders</td><td>30%</td><td>52%</td><td>68%</td><td><0.0001*</td></tr>
<tr><td>Secondary: change in UPDRS II+III</td><td>-2.2 <u>+</u> 10.2</td><td>-7.2 <u>+</u> 9.9</td><td>-11.0 <u>+</u> 10.5</td><td><0.0001*</td></tr>
<tr><td>Post-hoc: change in UPDRS II+III (study period)</td><td>____</td><td>-7.2 <u>+</u> 9.9</td><td>-9.0 <u>+</u> 10.4</td><td>P= 0.1336</td></tr>
<tr><td>Post-hoc: change in UPDRS II+III (24 weeks maintenance)</td><td>____</td><td>-8.4 <u>+</u> 10.1</td><td>-9.0 <u>+</u> 10.4</td><td>P= 0.5190</td></tr>
</table>
<u>* rotigotine compared to placebo and ropinirole compared to placebo both significant at p<0.0001</u>

Study Assessment:
• Intention-to-treat analysis
• Mentioned and met power
• Imbalanced titration and maintenance periods between treatment groups, making them hard to compare
• Did not show non-inferiority to ropinirole for the primary efficacy measure (not powered to show superiority)
• 92% of rotigotine patients tolerated doses of 8mg/24 hours, the maximum allowed dose. Only 26% of ropinirole patients received the maximum allowed dose of 24mg/day.
• Progression of PD estimated to be 3 UPDRS points per year, meaning that a longer study period is needed to examine true long-term effects.</td>
<td>Adverse Events:

<table>
<tr><th></th><th>Placebo %</th><th>Rotigotine %</th><th>Ropinirole %</th></tr>
<tr><td>ASR</td><td>11</td><td>38</td><td>7</td></tr>
<tr><td>Nausea</td><td>16</td><td>29</td><td>36</td></tr>
<tr><td>Somnolence</td><td>20</td><td>23</td><td>28</td></tr>
<tr><td>Dizziness</td><td>10</td><td>14</td><td>17</td></tr>
<tr><td>Vomiting</td><td>3</td><td>12</td><td>11</td></tr>
</table>
Serious Adverse Events:
Patients reported “sleep attacks,” including 6 patients treated with rotigotine and 4 patients treated with ropinirole.

Discontinuation due to adverse event:
Placebo – 5%
Rotigotine – 17%
Ropinirole – 13%</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Inclusion/Exclusion</th><th>Endpoints</th><th>Results/ Study Assessment</th><th>ADRs/Tolerability</th></tr>
<tr>
<td>CLEOPATRA-PD (Poewe, et al)[13]

MC, R, DB, DD, Placebo and pramipexole controlled

<u>Treatments</u>
Rotigotine (up to 16 mg/24 h transdermally), pramipexole (up to 4.5 mg/day orally), or placebo

<u>Duration</u>
Titration: up to 7 weeks
Maintenance: 16 weeks
Safety follow-up: 4 weeks</td>
<td><u>Inclusion</u>
30 years or older, PD by UK Brain Bank criteria, stable treatment with levodopa (minimum dose 300 mg/day), stable doses other antiparkinsonian medication, motor fluctuations of the wearing-off type with an average of at least 2.5 h per day spent in the “off ” state, graded no better than Hoehn and Yahr stage II when on and no worse than stage IV when off
<u>Exclusion Criteria</u>
Suspicion of atypical parkinsonism, previous surgery for Parkinson’s disease, mini-mental state examination score <25, concurrent hallucination or psychosis, history of orthostatic hypotension 6 mon. before baseline, history of MI over past 12 months, QTc interval >450 ms (men) or >470 ms (women), history of skin hypersensitivity to adhesives or other transdermals, intake of investigational drug within 4 wks before pretreatment visit. DAs, MAOIs, dopamine-releasing drugs, tolcapone, neuroleptics, cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, or quinine</td>
<td><u>Endpoints</u>
Primary:
1)absolute change in total hours “off ” (assessed by home diaries) from baseline to end of maintenance period
2)responder rate, defined as the proportion of patients with ≥30% reduction in absolute off time per day

Secondary:
changes from baseline to end of maintenance of the following: (1)absolute time spent on without troublesome dyskinesias, (2)number of off periods, (3)motor status after morning wake-up (on with or without troublesome dyskinesias or off), and (4)Unified Parkinson’s disease rating scale (UPDRS) II and III scores during on periods. Change in total levodopa dose and changes in duration of sleep (Parkinson’s disease sleep scale) were also evaluated.
Safety:
Included all who received at least one dose, ADE documentation, vital signs, labs, ECG, exams, Epworth sleepiness scale, exploratory, descriptive</td>
<td>Mean dose of rotigotine was 12.95 ± 3.54 mg/24 h
Mean dose of pramipexole was 3.1 ± 1.24 mg/day
96% of patients took levodopa
concomitant anti-parkinsonian medication in addition to levodopa:
placebo (43%)
rotigotine (52%)
pramipexole (53%)
Endpoints
<table><tr><th></th><th>Placebo n=101</th><th>Rotigotine n=204</th><th>Pramipexole n=201</th><th>P-value</th></tr><tr><td>Primary: abs change in “off” (hrs/day)</td><td>-0.9</td><td>-2.5</td><td>-2.8</td><td>p<0.0001*†
p=0.003€</td></tr><tr><td>responder rate</td><td>35.0%</td><td>59.7%</td><td>67.0%</td><td>p<0.0001*†
p=0.092€</td></tr><tr><td>Secondary: Abs time on w/out dyskinesias</td><td>1.4 ± 3.4</td><td>2.8 ± 3.5</td><td>2.7 ± 3.4</td><td>0.0003*
0.0007†
0.7980€</td></tr><tr><td>Off periods per day</td><td>–0.6 ± 1.8</td><td>–1.4 ± 1.8</td><td>–1.4 ± 1.9</td><td>0.001*
0.0006†
0.8478€</td></tr><tr><td>change in UPDRS II</td><td>–2.0 ± 4.3</td><td>–4.2 ± 4.5</td><td>–4.6 ± 4.4</td><td>p<0.0001*†
0.1874€</td></tr><tr><td>change in UPDRS III</td><td>–4.3 ± 9.3</td><td>–8.7 ± 8.0</td><td>–10.3 ± 8.7</td><td>p<0.0001*†
0.0672€</td></tr></table>*rotigotine vs. placebo
†pramipexole compared to placebo
€rotigotine compared to pramipexole

Significant differences were seen between both active treatments and placebo in status at morning wake-up and Parkinson’s disease sleep scale, but no difference between rotigotine and pramipexole.</td>
<td>Adverse Events:
<table><tr><th></th><th>Placebo %</th><th>Rotigotine %</th><th>Pramipexole %</th></tr><tr><td>ASR</td><td>9</td><td>18</td><td>6</td></tr><tr><td>Somnolence</td><td>8</td><td>12</td><td>12</td></tr><tr><td>Dizziness</td><td>4</td><td>6</td><td>10</td></tr><tr><td>Hallucinations</td><td>1</td><td>5</td><td>7</td></tr><tr><td>Orthostatic Hypotension</td><td>5</td><td>3</td><td>5</td></tr></table>Serious Adverse Events:
One report of sleep attack in pramipexole patient

Discontinuation due to ADR:
79 (16%) patients discontinued prematurely , most commonly because of adverse events:
14 (6%) in the pramipexole group
11 (5%) in the rotigotine group
6 (6%) in the placebo group
Study Assessment:
Used ITT analysis
Met power
Used pt diaries for measuring on/off time, may be subjective
Members of Schwarz Pharma, mfr of Neupro,® were involved in the steering committee for the trial design and responsible for ultimately submitting the manuscript for publication</td>
</tr>
</table>

Trial	Type of patients	Treatment	Time	Design	Endpoints	Results/Comments
Hening, et al[14]	Between 18 and 75 years old, diagnosis of RLS based on 4 cardinal features per International RLS Study Group (IRLSSG), ≥15 on IRLSSG Severity Rating Scale (IRLS), Clinical global impressions (CGI) score ≥4 on item 1 (severity of symptoms)	Randomly assigned in a 1:1:1:1:1 ratio Rotigotine 0.5mg/24 h (n=98) Rotigotine 1mg/24 h (n=99) Rotigotine 2mg/24 h (n=95) Rotigotine 3mg/24 h (n=103) Placebo (n=99)	4 week washout 4 week titration 6 month maintenance	R, DB, PC	**Primary Endpoints:** • Decrease in IRLS sum score from baseline to end of maintenance • Decrease in CGI item 1 score from baseline to end of maintenance **Secondary Endpoints:** • Proportion of treatment responders for IRLS score (50% improvement) • Proportion of treatment responders for CGI items 1 and 2 (50% improvement)	• Majority of patients had not previously been treated with dopaminergic agents for RLS. • 2mg/24 hours and 3mg/24 hours were superior to placebo in IRLS and CGI item 1 scores (P<0.001). • 0.5mg and 1mg/24 hours showed improvement in IRLS and CGI scores, but the differences were not statistically significant. • NNT for IRLS responder rate was 4.4 for the 2mg/24 hour rotigotine group. • NNT for IRLS responder rate was 3.4 for the 3mg/24 hour rotigotine group. • Application site reactions occurred more frequently in rotigotine-treated patients compared with placebo (27% vs. 5%). • Sleep attacks were reported for 9 patients in the rotigotine arm – 8 of which were determined to be drug related.
Trial	**Type of patients**	**Treatment**	**Time**	**Design**		**Results/Comments**
Trenkwalder, et al[15]	Between 18 and 75 years old, diagnosis of RLS based on 4 cardinal features per International RLS Study Group (IRLSSG), ≥15 on IRLSSG Severity Rating Scale (IRLS), Clinical global impressions (CGI) score ≥4 on item 1 (severity of symptoms). De novo patients (not previously treated with dopaminergic agents for RLS) as well as patients showing a positive response to a dopaminergic agent for RLS in the past, were included.	Randomized in a 1:1:1:1 ratio Rotigotine 2mg/24 hours (n=112) Rotigotine 2mg/24 hours (n=109) Rotigotine 3mg/24 hours (n=112) Placebo (n=114)	4 week washout 3 week titration 6 month maintenance	R, DB, PC	**Primary Endpoints:** • Decrease in IRLS sum score from baseline to end of maintenance • Decrease in CGI item 1 score from baseline to end of maintenance **Secondary Endpoints:** • Proportion of treatment responders for IRLS score (50% improvement) • Proportion of treatment responders for CGI items 1 and 2 (50% improvement)	• Three quarters of the sample were women, reflective of the greater incidence of RLS in females. • Both primary endpoints were statistically significantly improved in all 3 rotigotine groups compared to placebo by the end of maintenance phase. • Differences in primary endpoints were similar between de novo patients and those who had responded to dopaminergic medications previously. • 75% of rotigotine-treated patients rated the efficacy of the patch as “good” or “very good.” • 7% of patients in the placebo arm and 16% of rotigotine-treated patients discontinued the study drug prematurely due to adverse events, with the most common causes being application site reaction, vomiting, and nausea. • Sleep attacks were reported in 3 patients (2 rotigotine patients and 1 placebo patient).