Canadian Agency for Drugs and Technologies in Health

Issues in Emerging Health Technologies

Rotigotine Transdermal Patches (Neupro®) for the Treatment of Parkinson's Disease

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Summary

- ✓ **The rotigotine transdermal patch (Neupro®) is used for symptom control in Parkinson's disease.**
- ✓ **Study results indicate that rotigotine patches are effective in reducing the symptoms of early Parkinson's disease, and in reducing "off" time in advanced Parkinson's disease.**
- ✓ **Rotigotine patches offer the potential benefits of once-daily, topical administration and continuous drug delivery over 24 hours, which results in more constant drug levels than with oral medications. Transdermal administration (delivery of medication through the skin) may also benefit patients with difficulty swallowing.These features may improve adherence to drug therapy.**
- ✓ **The most common side effects with rotigotine patches are local skin reactions, nausea, sleepiness, dizziness, headache, vomiting, and insomnia.**

Background

Parkinson's disease is a neurodegenerative disorder, characterized by loss of the dopamine-producing neurons in the substantia nigra area of the brain, along with cell loss in other nerve pathways.[1,2] Dopamine is a neurotransmitter that regulates the transmission of signals in the brain. It affects many functions, including body movements, mood, and cognition.

The main clinical features of Parkinson's disease are tremor, muscular rigidity, akinesia (inability to move), and postural instability. Other features of the disease include changes in gait, mask-like face, micrographia (progressively smaller handwriting), and psychiatric symptoms; depression occurs in 50% of patients over the course of their illness.[3] The diagnosis is made by clinical symptoms and the patient's response to anti-parkinsonian drug treatment.[3]

Levodopa is the mainstay of therapy in Parkinson's disease, but it is associated with motor complications that affect 50% of patients after five years of treatment.[4-6] Levodopa-associated complications include dyskinesias (involuntary movements) and motor fluctuations or "on/off" episodes (alternating periods of improved versus poor or no motor function).[7] These side effects may result from pulsatile stimulation of the dopamine receptors. Transdermally administered medications that continuously stimulate the dopamine receptors may reduce these complications.[4,7,8]

The Technology

Rotigotine is a non-ergot dopamine agonist. The precise mechanism of action is not known, but it may be due to D_2-receptor stimulation in the caudate-putamen area of the brain.[9,10]

The rotigotine patch has three layers: a backing film, a drug matrix layer containing rotigotine, and a protective liner. The patch delivers rotigotine continuously over 24 hours.[9,11]

Regulatory Status

Rotigotine patches are not currently licensed for use in Canada.[12] The US Food and Drug Administration (FDA) approved rotigotine patches (Neupro®, UCB/Schwarz Pharma) in May 2007 for the treatment of early Parkinson's disease.[13]

Patient Group

Parkinson's disease affects about 100,000 Canadians. Most Canadians with this condition (about 85%) are over the age of 65 when diagnosed, but younger adults are also affected.[14,15] The prevalence of Parkinson's disease is expected to rise as Canada's population ages.[14]

Current Practice

Current treatments for Parkinson's disease control symptoms, but they do not halt or reverse the damage to dopamine-containing nerve cells. In the initial stages of the disease, drug therapy may not be needed. When symptoms become disabling, clinicians may delay using levodopa due to its risk of long-term motor complications and, instead, start patients on longer-acting oral dopamine

agonists (e.g., ropinirole, pramipexole).[16,17] However, levodopa is sometimes used in early, as well as in later, stages of the disease, as it offers effective symptom control, and other anti-Parkinson's drugs also have side effects.[18,19] Monoamine oxidase-B inhibitors (e.g., rasagiline and selegiline), which block dopamine metabolism, are also used as first-line therapy in the early stages of the illness.[17,19,20] When drug therapies fail to control symptoms in advanced Parkinson's disease, surgical interventions – such as deep brain stimulation – may be an option for some patients.[18,19]

The Evidence

Results from recent randomized controlled trials of rotigotine patches for Parkinson's disease are summarized in Table 1. Four of these trials[21-24] included individuals aged 30 or older without cognitive impairment, and with stages of physical disability that were mild to moderately severe, based on the Hoehn and Yahr scale (a five-stage scale of Parkinson's disease progression).[25] Compared to placebo, patients who used rotigotine transdermal patches showed statistically significant improvements in activities of daily living and motor function over baseline. It should be noted that in one study, the 2 mg/24 hours and 4 mg/24 hours rotigotine patches were not more efficacious than placebo.[23] The SURE-PD trial compared the mean improvement in Unified Parkinson's Disease Rating Scale (UPDRS) parts II (activities of daily living) and III (motor) scores with rotigotine to those with ropinirole (an oral dopamine agonist). The trial found rotigotine was inferior to ropinirole for this outcome.[24]

Two trials included patients aged 30 or older with advanced disease and motor fluctuations, and mild to severe disabilities on the Hoehn and Yahr scale.[26,27] In the PREFER study, patients showed a significant reduction in daily "off" time with rotigotine 8 mg and 12 mg per 24-hour strengths in comparison with patients who received placebo.[27] In the CLEOPATRA-PD trial, rotigotine was found to be noninferior to pramipexole for the average reduction in daily "off" time, but inferior to pramipexole in terms of response rate (defined as the percentage of individuals who achieved a ≥ 30% reduction in "off" time per day).[26]

While rotigotine patches were beneficial in early and advanced Parkinson's disease, these trials were limited by short maintenance phases which lasted from seven to 33 weeks.[21,22,24,26,27] A 2006 conference abstract reported preliminary results from an ongoing open-label extension trial of rotigotine in Parkinson's disease. Patients received a total of 85 weeks of rotigotine patch therapy. Most adverse reactions were mild, and patients demonstrated a sustained benefit in activities of daily living and motor function.[28] Several other trials of rotigotine patches, in early and advanced Parkinson's disease, and for other indications, are also underway.[29]

Adverse Effects

The most frequent adverse effects reported in 649 patients taking rotigotine were application-site reactions (37%), nausea (38%), sleepiness (25%), dizziness (18%), headache (14%), vomiting (13%), and insomnia (10%). Less frequent side effects included hallucinations, increased sweating, vertigo, dyspepsia, anorexia, back pain, arthralgias, fatigue, vertigo, and abnormal dreams.[9] One study reported sudden onset of sleep or loss of consciousness while driving in two patients, and reversible eosinophilia and neutropenia (blood disorders) in another subject.[23] Weight gain (>10% of baseline weight) occurred in 3% of patients taking rotigotine, as compared to <1% of patients on placebo. Fluid retention and the potential development of peripheral edema may be a concern in some patients.[9]

Administration and Cost

Rotigotine transdermal patches are available in the US in three strengths: 2 mg/24 hours, 4 mg/24 hours, and 6 mg/24 hours. The patch is applied once-daily to the skin of the abdomen, thigh, hip, flank, shoulder, or upper arm and left in place for 24 hours.[9]

A Canadian price for Neupro® is not yet available. In the US, the average wholesale price for a one-month supply of the 6 mg/24-hour strength rotigotine patches is US$281.82.[30] Monthly costs for other anti-Parkinson's drugs, based on US average wholesale prices, range from about US$50.00 to US$450.00.[31]

Concurrent Developments

Lisuride, another transdermal dopamine agonist, is also under investigation for the treatment of parkinsonian symptoms and dyskinesias.[32]

Spheramine® is a non-drug treatment for Parkinson's disease currently in clinical trials. It consists of human retinal pigment epithelial (hRPE) cells encapsulated in a gelatin micro-carrier that are implanted in the putamen area of the brain. These cells produce levodopa, the precursor of dopamine. In one report, six months after

Table 1: Recent randomized controlled trials of the rotigotine patch in Parkinson's disease	
Trial, Inclusion Criteria, Design, Treatment	**Outcome Measures, Results, Study Limitations**
The Parkinson Study Group, 2003 [23] **Inclusion criteria:** Early PD; anticholinergics, selegiline, and amantadine permitted. **Design:** R, DB, PC, MC, dose-ranging; n=242 **Treatment:** (Note: paper reported drug doses as content per patch, these have been converted here to equivalent nominal:doses as per other study reports.) • Rotigotine 2 mg/24 hours, n=49 • Rotigotine 4 mg/24 hours, n=47 • Rotigotine 6 mg/24 hours, n=48 • Rotigotine 8 mg/24 hours, n=51 • Placebo, n=47 4-week dose titration, 7-week maintenance, 1-week dose de-escalation, 2-week safety follow-up without study drug.	**Primary outcome*:** Change in sum of UPDRS scores parts II & III between baseline and end of treatment. • Mean changes in combined UPDRS scores (II & III): -0.29 for placebo, -1.20 for 2 mg rotigotine patch, -3.13 for 4 mg patch, -5.09 for 6 mg patch, & -5.3 for 8 mg patch. • Treatment effects (difference in mean change between rotigotine & placebo groups) on the combined UPDRS scores (II & III) were only statistically significant for the 6 mg patch (-4.83; 95% CI: -7.68 to -1.97; p=0.001) and 8 mg patch (-5.23; 95% CI: -8.02 to -2.44, p<0.001). **Study limitations:** Only data for North American patients are reported (n=242 of a total study enrollment of 329).
Jankovic et al, 2007 [21] **Watts et al, 2007** [22] (**Note:** Both articles report results from the same set of patients.) **Inclusion criteria**: Early PD; anticholinergics, MAOBs, and NMDA antagonists permitted. **Design:** R, DB, PC, MC; n=277 **Treatment:** • Rotigotine 2, 4 or 6 mg/24 hours, n=181 • Placebo, n=96 • 3 week-dose titration phase, 24 weeks maintenance, stepwise dose de-escalation every 2 days to 2mg/24 hours, safety follow-up 28 days later.	**Jankovic et al, 2007** [21] **Primary outcome:** Percentage of subjects with a ≥ 20% reduction in UPDRS scores (sum of parts II and III) from baseline. • 48% of the rotigotine group had ≥ 20% reduction in UPDRS score versus 19% for the placebo group (p<0.001); actual scores not reported. **Secondary outcomes:** QoL measures; improvement in the UPDRS scores (II and III). • Rotigotine group had non-significant improvements in QoL measures. • Statistically significant improvement in UPDRS score versus placebo at the end of maintenance phase – 15% mean reduction with rotigotine versus a 7.3% increase with placebo (p<0.002), actual scores were not reported. **Study limitations:** Only 273 of 277 randomized subjects were included in UPDRS secondary outcomes data. **Watts et al, 2007** [22] • **Primary outcome:** Change in UPDRS parts II and III (sum of scores) from baseline; analysis of responders (defined as ≥ 20% decrease in UPDRS score (parts II and III) from baseline). • Rotigotine patients had a mean decrease of 3.98 (± 7.07) in UPDRS scores versus a mean increase of 1.31(± 0.956) for placebo (p<0.0001) • 48% of the rotigotine group had ≥ 20% reduction in UPDRS score versus 19% for placebo (p<0.0001).
SURE-PD, 2007 [24] **Criteria:** Early PD; selegiline, amantadine, anticholinergic agents and CNS active drugs permitted. **Design:** R, DB, PC, DD, MC; n=561 **Treatment:** • Rotigotine 2, 4, 6 or 8 mg/24 hour, max. dose 8 mg/24 hours, n=215 • Oral ropinirole, 0.25, 0.5, 1.0, 2.0 or 5.0 mg 3xdaily, max. dose 24 mg/day; n=228 • Placebo, n=118 4-week titration period with rotigotine, 13-week titration with ropinirole (sham titration in other groups during this period; minimum 33-week maintenance phase for rotigotine, 24-week maintenance phase for ropinirole; safety follow-up at 4-weeks.	**Primary outcome:** ≥ 20% decrease in UPDRS II and III scores from baseline to end of DB maintenance phase. • 52% response rate with rotigotine patch compared with 30% for placebo, and 68% with ropinirole compared with placebo (p<0.0001 for both comparisons). **Secondary outcomes:** Absolute change in UPDRS II and III scores from baseline to end of DB maintenance phase; changes in UPDRS II & III subscale scores; demonstration of rotigotine noninferiority to ropinirole. • Mean decrease in UPDRS subtotal score: -7.2 (SD±9.9) for rotigotine compared with placebo, and -11.0 (SD±10.5) for ropinirole, -2.2 (SD±10.2) compared with placebo (p<0.0001 for both comparisons). • The noninferiority of rotigotine to ropinirole for the main efficacy outcomes was not shown. **Study limitations:** Four patients who were randomized were not included in the efficacy assessment.

Table 1: Recent randomized controlled trials of the rotigotine patch in Parkinson's disease (cont'd)	
Trial, Inclusion Criteria, Design, Treatment	**Outcome Measures, Results, Study Limitations**
PREFER study, 2007 [27] **Criteria:** Advanced PD for at least 3 years with bradykinesia & at least one other major symptom; not demented; taking at least 200 mg levodopa/day; anticholinergics permitted. **Design:** R, DB, PC, MC, PG; n=351 Treatment: • Rotigotine 8 mg/24 hours, n=120 • Rotigotine 12 mg/24 hours, n=111 • Placebo, n=120 5-week dose titration, 24-week maintenance.	**Primary outcome:** Change in absolute daily "off" time; percentage of responders (≥ 30% reduction in time spent off). • Rotigotine 8 mg group: average 2.7 hours reduction in daily "off" time (95% CI: -2.1,- 3.4; p<0.001), rotigotine 12 mg group: -2.1 hours reduction (95% CI: -1.5, -2.8; p<0.001), placebo: -0.9 hours reduction (95% CI: -0.32, -1.51; p>0.05).‡ • There were more responders in the rotigotine 8 mg (56.6%) & 12 mg groups (55.1%) than in the placebo group (34.5%) (p < 0.001 for both dosages relative to placebo) **Study limitations**: Although 351 subjects were randomized, 6 subjects were withdrawn for non-compliance, & only 341 included in ITT analysis for secondary outcomes.
CLEOPATRA-PD, 2007 [26] **Criteria:** Advanced PD; taking at least 300 mg levodopa/day; other anti-PD drugs permitted. **Design:** R, DB, DD, PC, MC; n=506 **Treatment:** • Rotigotine 4 – 16 mg/24 hours, n=204 • Pramipexole 0.375 – 4.5 mg/day, n=201 • Placebo n=101 Dose titration ≤ 7 weeks, 16 weeks maintenance, 6 days dose de-escalation, 4-week follow-up.	**Primary outcome**: Change in absolute daily "off" time; percentage of responders (defined as ≥ 30% reduction in "off" time from baseline to end of maintenance). • Mean change in daily "off" time vs. placebo was -1.58 hours for rotigotine (95% CI: -2.27, -0.90, p<0.0001) & -1.94 hours for pramipexole (95% CI: - 2.63, -1.25, p<0.0001); Rotigotine was non-inferior to pramipexole for this endpoint. • 59.7% of rotigotine patients responded (p<0.0001 vs. placebo), 67% of the pramipexole group responded (p<0.0001 vs. placebo), and 35% of the placebo group responded. Rotigotine was inferior to pramipexole for this end point. **Secondary outcomes**†**:**Changes from baseline to end in UPDRS II and III scores during "on" times. • UPDRS II and III scores were reduced in the drug groups compared to placebo (p<0.0001 for rotigotine or pramipexole vs. placebo). **Study limitations**: ITT analysis performed on 501 patients (5 randomized patients excluded for protocol violations).

CI=confidence interval; CNS=central nervous system; DB=double-blind; DD=double dummy; ITT=intention-to-treat; MAOB (monoamine oxidase-B inhibitor); MC=multicentre; n=number of subjects; NMDA=N-methyl-D-aspartate; PC=placebo-controlled; PD=Parkinson's disease; PG=parallel-group; R=randomized; QoL=quality of life; UPDRS=Unified Parkinson's Disease Ranking Scale (a standardized, six-part rating system for assessing Parkinson's disease: UPDRS II=activities of daily living, UPDRS III=motor); vs.=versus

* Secondary outcomes included change in UPDRS parts I, II, and III, and change in Hoehn and Yahr stage, but results were not reported with sufficient clarity to permit inclusion in the table.

† Secondary outcomes included change in absolute "on" time without troublesome dyskinesias, number of "off" times, and motor status upon awakening, but results were not reported with sufficient clarity to permit inclusion in the table.

‡ P-values are for the change from baseline within each group, not for comparisons between groups.

implanting the product in six patients with advanced Parkinson's disease, Unified Parkinson's Disease Ranking Scale motor scores and Dyskinesia Rating Scale scores improved in three patients.[33]

Rate of Technology Diffusion

Although the current US approval for rotigotine patches is for the treatment of early Parkinson's disease, its use will likely expand to include the treatment of motor fluctuations in patients with advanced disease.

A marketing application for the use of rotigotine patches in the treatment of moderate-to-severe restless legs syndrome has been submitted in Europe.[34] Recent trials reported improvements in symptom control and quality of life in patients with restless legs syndrome treated with rotigotine patches.[35,36]

Implementation Issues

Adherence to treatment when taking numerous drugs may be an issue for both patients and caregivers. The rotigotine patch may improve treatment adherence due to its ease of use and once-daily administration schedule. Improved adherence was reported in a retrospective survey of 114 patients taking rotigotine over an average of 70 weeks.[37] Transdermal administration may also be of benefit to patients unable to take oral medications, or those with swallowing difficulties due to advanced disease.[1,7]

If approved in Canada, rotigotine patches may be used in place of existing drug therapies in the treatment of some patients with early Parkinson's disease. Rotigotine patches may also be used as an adjunct to existing treatments, and use is likely to expand to patients in the later stages of Parkinson's disease. The most effective clinical role for rotigotine is not yet clear, nor is its potential impact on Parkinson's disease treatment costs.

Long-term studies are required to provide evidence that treatment with rotigotine patches is efficacious and safe over time, that it increases patient and caregiver adherence with drug therapy, and that it improves patients' quality of life.

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