PharmaNote®

Volume 28, Issue 2 November 2012

ROTIGOTINE: TRANSDERMAL DOPAMINE AGONIST FOR THE TREATMENT OF PARKINSON'S DISEASE

Alia Bakht Pharm.D. Candidate

Parkinson's disease (PD) affects an estimated four to six million people worldwide, with 60,000 new cases diagnosed each year in the US.[1,2] The average age of onset of Parkinson's disease is 62 years with complications caused by the disease rated as the 14th leading cause of death in the United States by the Center for Disease Control.[2] Parkinson's disease is a progressive neurodegenerative disorder costing patients an estimated $10,349 yearly, with the total annual economic cost of PD in the U.S. at $23 billion as of 2005.[3]

Restless leg syndrome (RLS) affects 7.3% of the population and is characterized primarily by a strong urge to move ones legs becoming worse at rest and at night, effecting sleep, work, relationships and health. RLS can be diagnosed at all ages but is most prevalent between the ages of 60 and 69, with women diagnosed twice as often as men.[4, 5] RLS sufferers have a significantly lower quality of health than unaffected individuals, as measured by the EuroQol 5-Dimension scale, and the condition costs an estimated $490.70 per individual sufferer annually with costs increasing with RLS severity.[4]

In 2007, UCB owned Schwarz Pharma gained FDA approval for Neupro® (rotigotine), a dopamine agonist transdermal patch, for the treatment of early PD and later gained approval for the treatment of advanced PD.[6, 7] In 2012, UCB gained FDA approval for Neupro® for the treatment of RLS. Rotigotine transdermal patch overcomes deficits in current therapy by providing continuous 24 hour dopaminergic stimulation, thereby avoiding the complications of pulsatile dosing, and by providing an alternate dosing route for patients with trouble swallowing.[1,8] The once daily dosing of the rotigotine patch should also benefit patient adherence.[1]

This article will review the pharmacology, pharmacokinetics, clinical trials, dosing and administration, adverse effects, safety issues and costs of rotigotine transdermal patch.

Pharmacology

Rotigotine is a non-ergot dopamine (DA) receptor agonist at D2 receptors but also has activity at subtypes D3, and D1. Additionally, rotigotine has agonist activity on serotonin subtype 1a receptors (5HT1A) and some α-2 antagonist properties.[8] The D1 and D2 receptors, located mainly in the striatum, are central to the treatment of PD, while D3 agonism has been shown beneficial in animal models.[1] Alpha-2 receptors modify dopamine transmission while 5HT1A agonists have anxiolytic properties.[1, 9] Rotigotine is the active (S)-(-)-enantiomer of a racemic mixture with high lipophilicity that allows for transdermal delivery .[1,10]

Parkinson's disease involves the progressive degeneration of the dopamine containing neurons in the substantia nigra and corpus striatum.[10] The motor-

Inside This Issue:

function complications of PD are believed to be a result of the pulsatile stimulation of these neurons with commonly used short acting agents, such as levodopa.[11] The effects of rotigotine in PD are believed to be related to stimulation of DA receptors in the caudate-putamen in the brain, but the exact mechanism of action of rotigotine in PD is unknown.[6] The continuous stimulation provided by transdermal rotigotine would avoid the complications of pulsatile dosing.[8]

The exact etiology of RLS is still unknown, but studies show reduced dopaminergic activity in the central nervous system.[1] It is hypothesized that rotigotine works in RLS through its ability to stimulate DA receptors, though it's exact mechanism of action remains unknown.[6]

Pharmacokinetics

Transdermal rotigotine has a bioavailability of 37% with similar plasma concentration profiles between the different suggested sites of application (**Table 1**).[1, 12] The transdermal form avoids first-pass hepatic and gut wall metabolism and absorption is not affected by food.[1, 6] Rotigotine has no characteristic peak concentration but the time to peak (T_{max}) is between 15-18 hours with steady state concentrations reached in 2-3 days with daily dosing.[6] There is a lag time of 3 hours to reach peak plasma concentrations when a new patch is applied but concentrations remain mostly stable over 24 hours.[1] Trough plasma concentrations increase linearly with increasing rotigotine plasma levels and decrease with a terminal half-life of 5-7 hours after patch removal.[1, 6]

Extensive metabolism of rotigotine occurs through conjugation and N-dealkylation. Rotigotine is also metabolized by various cytochrome P450 (CYP) isoenzymes, multiple sulfotransferases, as well as uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A9 and UGT2B15. In vivo testing showed that steady state pharmacokinetics were not affected by coadministration with cimetidine, a CYP 1A2, 2C19, 2D6 and 3A4 inhibitor. The multiple metabolic pathways for rotigotine make drug interactions possible, but likely clinically irrelevant.[1, 6] Rotigotine undergoes biphasic elimination and is primarily excreted as inactive conjugates of the parent compound and N-desalkyl metabolites with approximately 71% excreted in the urine and 23% in the feces. Eleven percent is renally eliminated as other metabolites and less than 1% is renally eliminated in the unconjugated form.[6]

Table 1 | Pharmacokinetic Properties of Transdermal Rotigotine [6,12]

Property	Data
Bioavailability	~37%
Time to T_{max}	15-18 h
Time to Steady State	2-3 days
Half-life (h)	5-7
Protein Binding (in vivo)	89.5%
Vd	84 L/kg
Metabolism	Conjugation, N-dealkylation
Excretion	~71% urine, ~23% feces

H = hours; T_{max}=time to peak concentration, Vd=volume of distribution

No dosage adjustments are needed in patients with mild to moderate renal or hepatic impairment. Similar plasma concentrations were seen between males and females and between patients age 65-80 and patients age 40-64. Kinetics have not been studied in patients greater than 80 or less than 18 years of age.[6]

Clinical Trials

FDA approval of rotigotine for PD was based on three parallel group, randomized, double-blind placebo-controlled trials conducted on early stage PD patients not receiving any other PD medications (**Table 2**). Efficacy was also established for advanced stage PD in two trials conducted on patients with advance PD taking concomitant levodopa therapy (Table 3).[6]

Early Stage Parkinson's Trials: PD-1, PD-2, PD-3

PD-1 was a randomized, multicenter, double-blind, placebo-controlled, parallel group, dose-ranging study conducted by the Parkinson Study Group to assess the efficacy and safety of rotigotine in early stage PD patients not receiving dopaminergic medications.[13] Patients were randomly assigned to one of five groups: placebo (n=47), 4.5 mg rotigotine patch (n=49), 9 mg rotigotine patch (n=47), 13.5 mg rotigotine patch (n=48), and 18 mg rotigotine patch (n=51). The 4.5 mg, 9 mg, 13.5 mg and 18 mg patches delivered 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h, respectively. The study included a 4 week dose titration period and a 7 week maintenance period for a total treatment time of 11 weeks. The main outcome measure was the change in sum of the scores of the Unified Parkinson's Disease Rating Scale (UPDRS) parts II and III (activities of daily living and motor components) from baseline to end of treatment. From baseline to week 11, the mean change in motor and ADL UPDRS scores were: placebo, 0.3 ± 7.7; 4.5 mg group, 1.2±6.5, (p=0.52); 9.0 mg group, 3.1 ± 6.4, (p=0.6); 13.5 mg group, 5.1 ± 7.0, (p=0.001); 18 mg group, 5.3 ± 7.0, (p<0.001). Results of the study showed a significant

dose-related improvement in scores for the two highest doses of rotigotine, 13.5 mg and 18 mg.[13]

A second study in early Parkinson's patients, PD-2, was a North American multicenter, randomized, double-blind study to compare the safety and efficacy of transdermal rotigotine and placebo.[14] The study consisted of 242 subjects randomized to two groups with the primary efficacy measures being change in the UPDRS part II and III sum scores from baseline to end of treatment and responder rates. Responders were defined as patients with ≥ 20% improvement in UPDRS sum scores. Patients received either placebo (n=96) or rotigotine (n=81). Rotigotine patients were started at a dose of 2 mg/24 h, titrated up to 6 mg/24 h and then maintained for 6 months. The mean absolute difference in UPDRS subtotal scores in patients treated with rotigotine was 5.28 ± 1.18 points lower than in those treated with placebo by the end of the study (p<0.0001). The rotigotine group had more responders than the placebo group, with responder rates of 48% and 19%, respectively (p<0.0001). By the end of the study, rotigotine showed significantly improved UPDRS sum scores and had significantly more responders as compared to placebo. [14]

A third multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled trial was conducted in Europe on 561 early stage PD patients to assess the efficacy and safety of transdermal rotigotine.[15] The primary outcome was the proportion of responders, defined as patients with a ≥ 20% decrease in UPDRS part II and III sum score. Patients were randomized to receive placebo (n=117), transdermal rotigotine (n=213), or oral ropinirole (n=227). All patients applied two patches daily and took capsules three times per day to maintain the double-dummy study design and all patients were titrated to either the optimal effective dose or the maximum permitted dose. Patients randomized to rotigotine were started on a dose of 2 mg/24 h and titrated in weekly increments of 2 mg/24 h with a maximum permitted dose of 8 mg/24 h. Patients randomized to ropinirole were started at 0.25 mg three times a day (tid) and were titrated in weekly increments of 0.25 mg tid with a maximum permitted dose of 24 mg/day. Responder rates were 52% in the rotigotine group and 30% in the placebo group (p<0.0001).[15]

Advanced Stage Parkinson's Trials: PREFER and CLEOPATRA

Two studies were conducted to demonstrate the efficacy of rotigotine in advanced stage PD patient's currently receiving levodopa therapy and experiencing wearing-off type motor fluctuations (**Table 3**).[16] The PREFER study was a randomized, double-blind, placebo-controlled trial in which 351 patients experiencing ≥ 2.5 hours of "off" time per day were randomized to either placebo or rotigotine 8 mg/2 4h or 12 mg/24 h. The primary efficacy measures were change

Table 2 | Summary of Rotigotine Trials in Patients with Early Stage Parkinson's Disease [13,14,15]

Study	Design	Intervention	Results
PD-1[13] Dose Response Study	R, DB, PCB-controlled, PG n= 242 1° outcome: Change in sum of UPDRS parts 2 and 3 BL to week 11	Patches: 4.5mg (2mg/24h), 9.0mg (4mg/24h), 13.5mg (6mg/24h) or 18.0 mg (8mg/24h) rotigotine or PCB for 11 weeks	1° outcome: PCB: 0.3±7.7 4.5mg group: 1.2±6.5, (p=.52) 9.0mg group: 3.1±6.4, (p=.06) 13.5mg group: 5.1±7.0, (p=.001) 18.0mg group: 5.3±7.0, (p<.001)
PD-2[14] North American Study	MC, R, DB n= 277 1° outcomes: (1) Change in UPDRS scores BL to end (2) RR (pts ≥ 20% improvement)	PCB or rotigotine 2mg/24h, titrated weekly to 6mg/24h and maintained for 6 months	1° outcomes: (1) Mean absolute difference of 5.28 (±1.18) points lower UPDRS score compared to PCB (p<0.0001) (2) RR: Rotigotine: 48% PCB: 19% p<0.0001
PD-3[15] Foreign Multinational Study	MC, MN, R, DB, DD, PCB- and ropinirole-controlled n=561 1° efficacy outcome: proportion responded to treatment (≥20% decrease in UPDRS scores BL to end of maint)	Rotigotine: 2mg/24h, titrated weekly by 2mg/24h*. Max 8mg/24h (min dose maint period 33 weeks) Ropinirole: 0.25mg tid, titrated weekly by 0.25mg tid*. Max 24mg/d (min dose maint period 24 weeks) or PCB* *Pts titrated to optimal effective or max permitted dose	1° efficacy outcome: Rotigotine patch responders: 52% PCB responders: 30% (p<0.0001)

1°=primary, BL=Baseline, d=day, DB=double blind, DD=double dummy, h=hours, maint=maintenance, MC=multicenter, min=minimum, MN=multinational, PCB=placebo, PG=parallel group, Pts=patients, R=randomized, RR= Responder rates, TID=three times daily, UPDRS=unified Parkinson's disease rating scale

Table 3 | Summary of Rotigotine Trials in Patients with Advance Stage Parkinson's Disease [16,17]

Study	Design	Intervention	Results
PREFER[16]	R, DB, 3-arm, PG n= 351 1° efficacy outcomes: (1)Change in daily "off" h from BL to end of week 24 (2) RR for ≥ 30% reduction in "off" time	PCB (n=120) Rotigotine up to: 8mg/24h (n=120) or 12mg/24h (n=111)	1° efficacy outcomes: (1) Decrease in mean off time compared to PCB: 8mg/24h: 1.8h/d 12mg/24h: 1.2h/d (2) RR: PCB: 34.5% 8mg/24h: 56.6% 12mg/24h: 55.1%
CLEOPATRA[17]	RCT n= 506 1° efficacy outcomes: (1) Absolute change in total h "off" compared to placebo (2) RR (≥30% reduction in absolute time off/day)	Rotigotine (up to 16mg/24hr transdermally) (n=204) Pramipexole (up to 4.5mg/day orally) (n=201) or PCB (n=101) For 6 months	1° outcomes: (1)Change off time compared to PCB: Rotigotine: -1.58h, (p<0.0001) Pramipexole: -1.94h, (p<0.0001) (2) PCB: 35% Pramipexole: 67% Rotigotine: 59.7%

1°=primary, BL=Baseline, d=day, DB=double blind, h=hours, PCB=placebo, PG=parallel group, R=randomized, RR= responder rates

Table 4 | Summary of Rotigotine Trials in Patients with Restless Leg Syndrome [18.19]

Study	Design	Intervention	Results
RLS-1[18]	R, DB, PCB-controlled n= 505 1° efficacy outcomes: Decrease BL to end in (1) IRLS sum score and (2) CGI-1 score	PCB or Rotigotine: 0.5mg/24h, 1mg/24h, 2mg/24h or 3mg/24h	1° efficacy outcomes: (1)Adjusted treatment differences to PCB for IRLS sum score: 0.5/24h dose: -2.2, (p=0.0682) 1mg/24h dose: -2.3, (p=0.0535) 2mg/24h dose: -4.5, (p=0.0002) 3mg/24h dose: -5.2, (p<0.0001) (2)Adjusted treatment differences to PCB for CGI-1 score: 0.5/24h dose: -0.35, (p=0.0602) 1mg/24h dose: -0.32, (p=0.0857) 2mg/24h dose: -0.65, (p=0.0007) 3mg/24h dose: -0.9, (p<0.0001)
RLS-2[19]	R, DB, PCB-controlled n= 458 1° efficacy outcomes: Absolute change BL to end of maintenance in (1) IRLS sum score and (2) CGI-1 score	PCB or Rotigotine 1mg/24h, 2mg/24h or 3mg/24h	1° outcomes: (1)Mean change in IRLS sum score: PCB: -8.6 (SE 0.9) 1mg/24h: -13.7 (0.9) 2mg/24h: -16.2 (0.9) 3mg/24h: -16.8 (0.9) (p<0.0001) (2)Mean change in CGI-1 score: PCB: -1.34(SE 0.14) 1mg/24h: -2.09 (0.14) 2mg/24h: -2.41 (0.14) 3mg/24h: -2.55 (0.14) (p<0.0001)

1°=primary, BL=baseline, CGI-1= clinical global impression, d=day, DB=double blind, h=hours, IRLS=International restless leg syndrome, PCB=placebo, R=randomized

in the number of "off" hours from start to baseline and the responder rate, responders being participants with ≥ 30% reduction in "off" hours from baseline. The change in number of "off" hours from start to baseline compared to placebo were 1.8 hours/day for rotigotine 8 mg/24 h (p<0.0001) and 1.2 hours/day for rotigotine 12 mg/24 h (p=0.0031). The responder rates were as follows: placebo, 34.5%; 8 mg/24 h rotigotine, 56.6%; 12 mg/24 h rotigotine, 55.1%. The study found that rotigotine significantly reduced patients' number of "off" hours.[16]

The CLEOPATRA-PD trial was a randomized control trial in which 506 patients were randomized to receive either placebo (n= 101), rotigotine (n= 204) or pramipexole (n= 201) to assess the primary outcomes of absolute change in hours "off" from baseline to end of study and responder rate, responders being participants with ≥ 30% reduction in off hours from baseline.[17] Patients were titrated to maximum efficacy and tolerability up to either 16 mg/h rotigotine transdermal patch or 4.5 mg/d pramipexole during a 7 week titration phase, and then remained on a steady dose for a 16 week maintenance period. Compared to placebo, the mean change in off time from baseline was -1.5 hours for rotigotine (p<0.0001) and -1.94 hours for pramipexole (p<0.0001). Responder rates were as follows: placebo, 35%; rotigotine, 59.7%; pramipexole, 67%. Study findings showed that rotigotine was non-inferior to pramipexole for reducing absolute "off" time. [17]

RLS Trials: RLS-1 and RLS-2

FDA approval for transdermal rotigotine for restless leg syndrome was based on two fixed-dose, double-blind, randomized, placebo-controlled trials with six month maintenance periods (**Table 4**).[6]

RLS-1 was a randomized, double-blind, placebo-controlled trial in 505 patients with moderate to severe RLS who were randomly assigned to one of five groups to assess the safety and efficacy of transdermal rotigotine in treating idiopathic RLS.[18] The primary outcome measures were the change in International RLS (IRLS) sum score and clinical global impression (CGI-1) score. Patients were randomized to receive either placebo or rotigotine 0.5, 1, 2, or 3 mg/24 h transdermally over a 6 month maintenance period. Adjusted treatment differences to placebo for IRLS sum score were as follows: rotigotine 0.5 mg/24 h, -2.2, (p=0.0682); rotigotine 1 mg/24 h, -2.3, (p=0.0535); rotigotine 2 mg/24 h, -4.5, (p=0.0002); rotigotine 3 mg/24 h, -5.2, (p<0.0001). Adjusted treatment differences to placebo for CGI-1 score were: rotigotine 0.5 mg/24 h, -0.35, (p=0.0603); rotigotine 1 mg/24 h, -0.32, (p=0.0857); rotigotine 2 mg/24 h, -0.65, (p=0.0007); rotigotine 3 mg/24 h, -0.9, (p<0.0001). Study findings showed rotigotine 2 and 3 mg/24 h to be superior to placebo for both measures (p<0.0001).[18]

RLS-2 was a randomized, double-blind, placebo-controlled trial in 458 patients with moderate to severe RLS who were randomized to one of four groups to investigate the efficacy of transdermal rotigotine for RLS over 6 months.[19] Patients were randomized to receive placebo or rotigotine 1, 2, or 3 mg/24 h with primary outcome measures being change in IRLS sum score and CGI-1 score from baseline to end of the maintenance period. Mean changes in IRLS sum scores from baseline to end of study were: placebo, -8.6 (Standard error (SE) 0.9); rotigotine 1 mg/24 h, -13.7 (0.9); rotigotine 2 mg/24 h, -16.2(0.9); rotigotine 3 mg/24 h, -16.8(0.9). Mean changes in CGI-1 score from baseline to end of study were as follows: placebo, -1.34 (SE 0.14); rotigotine 1 mg/24 h, -2.09(0.14); rotigotine 2 mg/24 h, -2.41(0.14); rotigotine 3 mg/24 h, -2.55(0.14), with p<0.0001 for all treatment differences versus placebo. Study findings showed transdermal rotigotine to be superior to placebo for both outcome measures.[19]

Adverse Events and Safety Issues

Adverse reactions were recorded across various clinical trials, with the most common being application site reaction and typical dopaminergic side effects (**Table 5**). Rotigotine also contains a sulfite group and may cause an allergic reaction in sulfite sensitive patients. One study showed that 2% of patients taking rotigotine 3nmg/24 h experienced sleep attacks, which are episodes of falling asleep during daily activities without any warning. Due to sleep attacks and the more commonly seen somnolence, patients are advised to drive and operate machinery with caution when first starting rotigotine during dose titration. There are reported instances of hallucinations, psychosis and dyskinesia in patients taking rotigotine and it is therefore advised that patients with preexisting psychiatric conditions avoid taking rotigotine. Rotigotine use has been linked to problems with impulse control and compulsive behavior and patients should be monitored for these events appropriately. Dopaminergic medications, such as rotigotine, may also lead to augmentation and rebound RLS. Augmentation is a worsening of symptoms or an onset of symptoms earlier in the day than before treatment was started. Rebound RLS is an exacerbation of symptoms caused by the wearing off of dopaminergic medications.[6]

Dosing and Administration

Table 5 | Most Commonly Observed Adverse Reactions (≥5% greater than placebo) for Highest Recommended Rotigotine Dose in Populations Studied [6]

Study Population	Early stage PD	Advanced stage PD	Restless Leg Syndrome
Highest Recommended Dose	6 mg/24 h	8 mg/24 h	3 mg/24 h
Adverse Reactions	Nausea (35%*) Vomiting (17%) Somnolence (16%) Application site reactions (15%) Dizziness (11%) Anorexia (8%) Hyperhidrosis (8%) Insomnia (5%)	Application site reactions (23%) Nausea (9%) Peripheral edema (8%) Dizziness (8%) Dyskinesia (7%)	Application site reactions (39%) Nausea (11%) Somnolence (6%) Headache (5%)

* Percentages represent percent occurrence greater than placebo
PD=Parkinson's Disease

Rotigotine transdermal is available in 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, and 8 mg per 24 hour systems. Rotigotine transdermal patch should be applied once daily to clean, dry, non-oily, intact healthy skin. The patch should be applied at the same time every day in an area where it will not be directly rubbed by clothing or exposed to direct heat or prolonged sunlight. The patch can be applied to the abdomen, thigh, hip, flank, shoulder or upper arm. The application site should be changed on a daily basis and a patch should not be applied to the same spot more often than once every 14 days.[6]

Starting dose for patients with early stage PD is 2 mg/24 h and the dose can be titrated weekly by 2 mg/24 h as needed and as tolerated to a highest recommended dose of 6 mg/24 h. Patients with advanced stage PD should be started on an initial dose of 4 mg/24 h and can be titrated weekly by 2 mg/24 h as needed and tolerated to a maximum recommended dose of 8 mg/24 h. Patients with RLS should be started on a rotigotine dose of 1 mg/24 h and can be titrated by 1 mg/24 h as needed and tolerated with a highest recommended dose of 3 mg/24 h. When stopping rotigotine, the dose should be tapered down to prevent possible emergent withdrawal. For PD the dose should be decreased by a maximum of 2mg/24h every other day and for RLS the dose should be decreased by a maximum of 1mg/24h every other day until complete withdrawal.[6]

Summary

Rotigotine transdermal patches provide patients with Parkinson's disease and restless leg syndrome with continuous dopaminergic stimulation in a simple, once daily dosage form. Clinical studies have shown transdermal rotigotine to be superior to placebo in treating PD and RLS and to be non-inferior to some existing PD therapies with a fairly well tolerated side effect profile. Common side effects to rotigotine transdermal patch include application site reaction, nausea, and somnolence.

References

1. Splinter M. Rotigotine: Transdermal Dopamine Agonist Treatment of Parkinson's Disease and Restless Legs Syndrome. Ann Pharmacother 2007;41:285-95
2. National Parkinson's Foundation. http://www.parkinson.org/ (Accessed May 2012)
3. Huse D, MA, Schulman K, et al. Burden of Illness in Parkinson's Disease. Mov Disord 2005;20:1449-54
4. Allen R. Prevalence and Disease Burden of Primary Restless Legs Syndome: Results of a General Population Survey in the United States. Mov Disord 2011;26:114-20
5. RLS Foundation. http://www.rls.org/ (Accessed May 2012)
6. Neupro® (rotigotine) [Package Insert]. Smyrna, GA;UCB Inc.; 2012.
7. CenterWatch. http://www.centerwatch.com/ (Accessed May 2012)
8. Jenner P. A Novel Dopamine Agonist for the Transdermal Treatment of Parkinson's Disease. Neurology 2005;65(Suppl 1):S3-S5
9. Sanders-Bush E, Hazelwood L. Chapter 13. 5-Hydroxytryptamine (Serotonin) and Dopamine. In: Chabner BA, Brunton LL, Knollman BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12nd ed. New York: McGraw-Hill; 2011. http://www.accesspharmacy.com.lp.hscl.ufl.edu/content.aspx?aID=16662305. Accessed May 22, 2012.
10. Chen JJ, Swope DM, Dashitpour K, Lyons KE. Transdermal Rotigotine: A Clinically Innovative Dopamine-Receptor Agonist for the Management of Parkinson's Disease. Pharmacotherapy 2009;29:1452-67.
11. Chase TN. The Significance of Continuous Dopaminergic Stimulation in the Treatment of Parkinson's Disease. Drugs 1998;55(Suppl 1):1-9
12. Santiago P, Rey M, Ratti P, Rascol O. Rotigotine Transdermal Patch for the Treatment of Parkinson's Disease. Fundamental and Clinical Pharmcology 2012; 1-15
13. The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. Arch Neurol 2003;60:1721-8.
14. Watts RL, Jankovic J, Waters C, et al. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. Neurology. 2007; 68:272-6.
15. Giladi N, Boroojerdi B, Korcxyn AD, Burn DJ, Clarke CE, Schapira AH. Rotigotine transdermal patch in early Parkinson's disease: a randomized, double-blind, controlled study versus placebo and ropinirole. Mov Disord 2007;22:2398-404.
16. LeWitt PA, Lyons KE, Pahwa R; SP 650 Study Group. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. Neurology 2007; 68: 1262-7.
17. Poewe WH, Rascol O, Quinn N, et al.; SP 515 Investigators. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomized controlled trial. Lancet Neurol 2007;6:475-6.
18. Hening WA, Allen RP, Ondo WG, Walters AS, Winkelman JW, Becker P,

et al. Rotigotine improves restless legs syndrome: A 6-month randomized, double-blind, placebo-controlled trial in the United States. Mov Disord 2010 Aug 15;25:1675-83
19. Trenkwalder C, Benes H, Poewe W, Oertel WH, Garcia-Borreguero D, de Weerd AW, et atl. Efficacy of rotigotine for treatment of moderate -to-severe restless legs syndrome: a randomized, double-blind, placebo-controlled trial. Lancet Neurol 2008;7:595-604.

Clinical Trial Update

Hormone replacement therapy in recently post-menopausal women—Results of the Women's Health Initiative (WHI)[1] showed no cardiovascular (CV) benefit with hormone replacement therapy (HRT) in post-menopausal women. Post-hoc analysis suggested the benefits of HRT may be altered by the age at which therapy is initiated ("timing effect").

Schierbeck and colleagues investigated the long-term CV effects of HRT in women who were recently post-menopausal.[2] Healthy Danish women aged 45-58 were randomized to open label HRT (n=502) or placebo (n=504). HRT consisted of triphasisc 17-β-estradiol and norethisterone acetate for those with an intact uterus and monophasic 17-β-estradiol for those with a previous hysterectomy. Inclusion criteria were healthy, post-menopausal women with last menstrual bleeding 3-14 months prior to study entry or perimenopausal symptoms in combination with recorded serum follicle stimulating hormone values (>2 standard deviations [SD] above pre-menopausal mean). Key exclusion criteria include uncontrolled chronic disease, previous or current cancer or thromboembolic disease, and current or former use of HRT within the last three months.

The mean age of the participants was 49.7 years (SD 2.8 years), mean body mass index of 25.2 (SD 4.4), and a mean time since menopause of 0.59 years (SD 0.64 years). Study groups were well matched at baseline with the exception of age; women in the intervention group were on average 0.47 years younger (p=0.006).

The primary outcome was the composite of death, admission for myocardial infarction (MI), or heart failure (HF). The study was planned to continue for 20 years but was stopped at 10 years following publication of the results of the WHI[1] although participants were followed for an additional 6 years through national registries.

After 10 years HRT reduced the incidence of the primary endpoint compared to placebo (Hazard ratio [HR] 0.48, 95% Confidence Interval [CI] 0.26-0.87), even when adjusted for age (HR 0.49, 95% CI 0.27-0.89). Individual rates of death, MI, or HF did not differ statistically between groups, although were reduced with HRT. The incidence of stroke, deep vein thrombosis, or pulmonary embolism was also not different between groups, although rates of thromboembolism were low. Importantly, the rate of any cancer did not differ between groups (HR 0.92, 95% CI 0.58-1.45) and the rate of breast cancer (HR 0.58, 95% CI 0.27-1.27) was not increased with HRT; low incidence rates may have affected the results. Results were not different after 6 years of additional follow-up from those at 10 years.

The authors noted potential limitations such as low incidence rates of specific outcome and safety events, potential for insufficient follow-up time to observe all outcomes of interest, and that potentially healthy women may have a reduced incidence of adverse events.

Notably, women in the present study were much younger than the participants of the WHI (mean age of 50 vs. 64 years, respectively), and they were started on HRT much sooner (0.7 vs. 10 years, respectively). The type of estrogen/progestin may have also influenced the discordant results seen between the present study and the WHI.

The results indicate that HRT may be beneficial for healthy women aged 45-58 years in reducing the risk for future CV events if it is started soon after the onset of menopause without increasing the risk for thromboembolism, cancer, or stroke.

1. Rossouw JE, et al. JAMA 2002;288:321-33.
2. Scheierbeck LL, et al. BMJ 2012; doi:10.1136/bmj.e6409.

The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacotherapy and Translational Research
University of Florida