Drug Use Research & Management Program
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Class Update: Parkinson's Drugs

Month/Year of Review: September 2014
PDL Class: Parkinson's Drugs
Literature Search End Date: July 2014

Date of Last Review: September 2013
Source Document: OSU College of Pharmacy

Current Preferred Agents	Current Non-Preferred Agents
Anticholinergics	
Beztropine tablets	
Trihexyphenidyl tablets/exlixir	
COMT* Inhibitors	
Entacapone tablets	Tolcapone (Tamsar®) tablets
Dopaminergic Agents	
Carbidopa/Levodopa tablets	
Carbidopa/Levodopa ER tablets	
Dopamine Agonists	
Amantadine capsules/syrup/tablets	Bromocriptine (Parlodel®) tablets/capsules
Pramipexole DI-HCL tablets	Ropinirole (Requip®) IR and XL tablets
	Neupro transdermal
MAO- B** Inhibitors	
Selegiline capsules	Rasagaline (Azilect®) tablets
Combination Product	
Carbidopa/Levodopa/Entacapone	

*COMT = Catechol-O-methyl transferase; **MAO-B = Monoamine oxidase B

Previous Conclusions and Recommendations:

- Evidence does not support a difference in efficacy or effectiveness.
- Make tolcapone non-preferred due to reported liver toxicity
- Make carbidopa/levodopa ER preferred on PDL.
- There is insufficient evidence that rotigotine is more efficacious or safer than other oral dopamine agonists in the treatment of PD. It may be a reasonable option for patients with difficulty swallowing that may be addressed by use of the patch. Make rotigotine transdermal (Neupro) non-preferred on the PDL.

PA Criteria: All non-preferred agents require prior authorization to cover preferred products when feasible for covered diagnosis (**Appendix 1**). OHP does not cover treatment for restless leg syndrome.

Recommendations:

- No further research or review needed at this time.
- Evaluate Comparative costs in executive session.

Methods:
A MEDLINE OVID search was conducted using all treatments for Parkinson's disease (PD) and limited to randomized controlled trials and meta-analysis, English language, and conducted in humans since the date of the literature search conducted for the previous OHA P & T review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Systematic Reviews:
None

Guidelines:
None
New drugs:
None

New FDA Indications:
None

New FDA safety alerts:
None

New Trials:
A total of 61 citations resulted from initial literature search. After inclusion for further review, 10 were evaluated further and 5 potentially relevant comparative randomized trials were identified through abstract review for appropriate medication, indication, study design, and outcomes (**Appendix 2**). These trials are briefly described in Tablet 1.

Table 1: Potential Relevant New Trials

Study	Comparison	Population	Primary Outcome	Results
Schapira AH et al.[1], 2013	Pramipexole (1.5mg/day; N = 261) vs. placebo (N = 274); then at 6 or 9 months placebo group was given parmipexole.	PD diagnosed within 2 years at time of enrollment and aged 30 to 79 years.	15-month change from baseline in total score on Unified Parkinson's Disease Rating Scale (UPDRS).	At 15 months (n=411), adjusted mean change in UPDRS total score showed no significant difference between early and delayed pramipexole (-0·4 points, 95% CI -2·2 to 1·4, p=0·65).
Mizuno Y, et al.[2], 2013	Rotigotine patch (N = 82) vs. placebo (N = 90).	Early stage PD patients in Japan.	The change in UPDRS part II (activity of daily living) and part III (motor function) scores from baseline to the end of treatment (12 weeks)	The mean (± standard deviation) changes in UPDRS part II and III scores were -8.4 ± 9.7 in the rotigotine group and -4.1 ± 8.2 in the placebo group and were significantly different (P = 0.002).
Ory-Magne F, et al.[3], 2014	Wash-out study comparing continuation of amantadine (N = 27) vs. discontinuation of	Dyskinetic patients with PD on amantadine at least	The change from baseline in a UPDRS dyskinesia subscore (item 32 [duration] + 33 [severity]).	UPDRS items 32 + 33 deteriorated more in patients switched to placebo ("discontinuing" group) (+1.7 ± 2.0 units; 95% confidence interval 0.9, 2.4) as compared with those maintained on

	amantadine (N = 29).	200mg/day for at least 6 months.		amantadine ("continuing" group) (+0.2 ± 1.5 units; 95% confidence interval -0.4, 0.8; p = 0.003).
Zhang L, et al.[4], 2013	Rosagiline (1mg/day; N = 119) as adjunctive therapy to levodopa vs. placebo (N = 125).	PD patients with motor fluctuations in China.	The changes in “On” and “Off” time while awake between baseline and the week 12 visit using patient diary score cards.	The primary efficacy variable--mean adjusted total daily off time--decreased from baseline by 1.7 h in patients treated with 1.0 mg/d rasagiline compared to placebo ($p < 0.05$).
Zhang Z, et al.[5], 2013	Ropinirole XL (N = 175) as add-on therapy to Levodopa vs. placebo (N = 170).	Advanced PD not optimally controlled with Levodopa in China.	The change from baseline in awake time spent “Off” at week 24.	Subjects receiving ropinirole XL experienced a significant reduction of "off" time (2.1 h) compared with placebo (0.4 h); mean change of -1.7hr (95% CI: -2.27, -0.26; $p < 0.001$).

References:

1. Schapira AHV, McDermott MP, Barone P, et al. Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial. *Lancet Neurol*. 2013;12(8):747-755. doi:10.1016/S1474-4422(13)70117-0.

2. Mizuno Y, Nomoto M, Kondo T, et al. Transdermal rotigotine in early stage Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Mov Disord*. 2013;28(10):1447-1450. doi:10.1002/mds.25537.

3. Ory-Magne F, Corvol J-C, Azulay J-P, et al. Withdrawing amantadine in dyskinetic patients with Parkinson disease: the AMANDYSK trial. *Neurology*. 2014;82(4):300-307. doi:10.1212/WNL.0000000000000050.

4. Zhang L, Zhang Z, Chen Y, et al. Efficacy and safety of rasagiline as an adjunct to levodopa treatment in Chinese patients with Parkinson's disease: a randomized, double-blind, parallel-controlled, multi-centre trial. *Int J Neuropsychopharmacol*. 2013;16(7):1529-1537. doi:10.1017/S1461145713000175.

5. Zhang Z, Wang J, Zhang X, et al. The efficacy and safety of ropinirole prolonged release tablets as adjunctive therapy in Chinese subjects with advanced Parkinson's disease: a multicenter, double-blind, randomized, placebo-controlled study. *Parkinsonism Relat Disord*. 2013;19(11):1022-1026. doi:10.1016/j.parkreldis.2013.07.009.

Appendix 1: Current PA Criteria

Anti-Parkinsons Agents

Goal(s):

- Cover preferred products when feasible for covered diagnosis. Preferred products are selected on evidence based reviews.
- OPH does not cover treatment for restless leg syndrome (Coverage line 624)

Length of Authorization: 12 months

Requires PA:
Non-preferred drugs

Covered Alternatives:
Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis Parkinson's disease or another chronic neurological condition?	**Yes:** Go to #5.	**No:** Go to #3
3. Is the diagnosis Restless Leg Syndrome (ICD9-333.94)? *Baseline therapy is defined as being on ≥1 stable dose of an anti-epileptic(s) drug for at least 4 weeks.	**Yes:** Pass to RPH; Deny, (Not covered by OHP)	**No:** Go to #4
4. RPH only All other indications need to be evaluated as to whether they are above the line or below the line	**Above:** Go to #5	**Below:** Deny, (Not covered by the OHP)
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class.	**No:** Approve for the shorter of 1 year or length of prescription

DUR/P&T Board Action: 9/06/10 (DO)
Revision(s):
Initiated: 1/1/11

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Appendix 2: Randomized Clinical Trials

1. **Schapira AHV, McDermott MP, Barone P, et al. Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial. *Lancet Neurol*. 2013;12(8):747-755.**

Abstract

Background: In models of dopaminergic neuronal loss, the dopamine agonist pramipexole has exhibited neuroprotective properties. The Pramipexole On Underlying Disease (PROUD) study was designed to identify whether early versus delayed pramipexole initiation has clinical and neuroimaging benefits in patients with Parkinson's disease (PD).

Methods: Between May 24, 2006, and April 22, 2009, at 98 centres, we recruited patients with PD diagnosed within 2 years and aged 30-79 years. We randomly assigned eligible patients (ratio 1:1), by a centralised, computerised randomisation schedule, to receive double-blind either placebo or pramipexole (1·5 mg a day) and followed them up for 15 months. At 9 months, or as early as 6 months if considered necessary, placebo recipients were assigned to pramipexole. In a neuroimaging substudy, striatal dopamine-transporter binding was assessed by SPECT. All patients, investigators, and independent raters were masked to study treatment. The primary endpoint was the 15-month change from baseline in total score on the unified Parkinson's disease rating scale (UPDRS).

Findings: Of 535 patients, 261 were randomly assigned to receive pramipexole and 274 to receive placebo. At 15 months (n=411), adjusted mean change in UPDRS total score showed no significant difference between early and delayed pramipexole (-0·4 points, 95% CI -2·2 to 1·4, p=0·65). 62 patients in the early pramipexole group and 61 patients in the delayed pramipexole group were included in the neuroimaging substudy, for which the adjusted mean 15-month change in striatal (123)I-FP-CIT binding was -15·1% (SE 2·1) for early and -14·6% (2·0) for delayed pramipexole (difference -0·5 percentage points, 95% CI -5·4 to 4·4, p=0·84). Overall, 180 (81%) of patients given early pramipexole and 179 (84%) patients given delayed pramipexole reported adverse events (most frequently nausea), and 22 (10%) patients in the early pramipexole group and 17 (8%) in the delayed pramipexole group had serious events, two of which (hallucinations and orthostatic hypotension) were deemed related to study drug.

Interpretation: By clinical and neuroimaging measures, pramipexole showed little evidence differentiating 15-month usage from usage delayed for 6-9 months. The results do not support the hypothesis that pramipexole has disease-modifying effects.

2. **Mizuno Y, Nomoto M, Kondo T, et al. Transdermal rotigotine in early stage Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Mov Disord*. 2013;28(10):1447-1450.**

Abstract

Background: We conducted a randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of transdermal rotigotine at doses up to 16 mg/24 hours in patients with early stage Parkinson's disease (PD) in Japan.

Methods: Patients received once-daily rotigotine 2 to 16 mg/24 hours (mean dose, 12.8 mg/24 hours; n = 82) or placebo (n = 90) for 12 weeks. The primary endpoint was the change in Unified Parkinson's Disease Rating Scale (UPDRS) part II (activities of daily living) and part III (motor function) scores from baseline to the end of treatment.

Results: The mean (± standard deviation) changes in UPDRS part II and III scores were -8.4 ± 9.7 in the rotigotine group and -4.1 ± 8.2 in the placebo group and were significantly different (P = 0.002). More patients in the rotigotine group than in the placebo group had a ≥ 20% score reduction. No serious drug-related adverse events were reported.

Conclusions: Rotigotine at doses up to 16 mg/24 hours was well tolerated and improved function in patients with early stage PD.

3. **Ory-Magne F, Corvol J-C, Azulay J-P, et al. Withdrawing amantadine in dyskinetic patients with Parkinson disease: the AMANDYSK trial. *Neurology*. 2014;82(4):300-307.**

Abstract

Objective: The AMANDYSK trial was designed to assess long-term efficacy of chronic treatment with amantadine in patients with Parkinson disease (PD) and levodopa-induced dyskinesia (LID).

Methods: This was a 3-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group, wash-out study conducted in 57 amantadine-treated (≥200 mg/d for ≥6 months) dyskinetic patients with PD. The primary outcome measure was the change from baseline in a Unified Parkinson's Disease Rating Scale (UPDRS) dyskinesia subscore (items 32 [duration] + 33 [severity]). Secondary outcomes included other LID measurements ("responders" analysis, premature dropout for LID, Abnormal Involuntary Movement Scale). Exploratory outcomes included time with troublesome dyskinesia as measured by diaries, UPDRS Motor Examination (part III) for motor symptoms of PD, and fatigue and apathy scores for nonmotor symptoms.

Results: UPDRS items 32 + 33 deteriorated more in patients switched to placebo ("discontinuing" group) (+1.7 ± 2.0 units; 95% confidence interval 0.9, 2.4) as compared with those maintained on amantadine ("continuing" group) (+0.2 ± 1.5 units; 95% confidence interval -0.4, 0.8; p = 0.003). Secondary outcomes confirmed this difference because there were significantly more responders, more dropouts for LID, greater increase in "ON" time with troublesome dyskinesia, and greater worsening of Abnormal Involuntary Movement Scale score in the discontinuing group. There were no between-group differences in the UPDRS Motor Examination, whereas apathy (as measured by caregivers) and fatigue scores tended to worsen more in patients randomized to placebo.

Conclusion: Wash-out of amantadine in dyskinetic patients with PD significantly worsened LID. No significant effect was observed on motor parkinsonian symptoms, while exploratory outcomes suggested that amantadine might improve apathy and fatigue in such patients.

Classification of evidence*:* This article provides Class II evidence that in patients with PD, withdrawing amantadine significantly aggravates LID in a median time of 7 days.

4. **Zhang L, Zhang Z, Chen Y, et al. Efficacy and safety of rasagiline as an adjunct to levodopa treatment in Chinese patients with Parkinson's disease: a randomized, double-blind, parallel-controlled, multi-centre trial. *Int J Neuropsychopharmacol*. 2013;16(7):1529-1537.**

Abstract

Rasagiline mesylate is a highly potent, selective and irreversible monoamine oxidase type B (MAOB) inhibitor and is effective as monotherapy or adjunct to levodopa for patients with Parkinson's disease (PD). However, few studies have evaluated the efficacy and safety of rasagiline in the Chinese population. This study was designed to investigate the safety and efficacy of rasagiline as adjunctive therapy to levodopa treatment in Chinese PD patients. This was a randomized, double-blind, placebo-controlled, parallel-group, multi-centre trial conducted over a 12-wk period that enrolled 244 PD patients with motor fluctuations. Participants were randomly assigned to oral rasagiline mesylate (1 mg) or placebo, once daily. Altogether, 219 patients completed the trial. Rasagiline showed significantly greater efficacy compared with placebo. During the treatment period, the primary efficacy variable--mean adjusted total daily off time--decreased from baseline by 1.7 h in patients treated with 1.0 mg/d rasagiline compared to placebo ($p < 0.05$). Scores using the Unified Parkinson's Disease Rating Scale also improved during rasagiline treatment. Rasagiline was well tolerated. This study demonstrated that rasagiline mesylate is effective and well tolerated as an adjunct to levodopa treatment in Chinese PD patients with fluctuations.

5. **Zhang Z, Wang J, Zhang X, et al. The efficacy and safety of ropinirole prolonged release tablets as adjunctive therapy in Chinese subjects with advanced Parkinson's disease: a multicenter, double-blind, randomized, placebo-controlled study. *Parkinsonism Relat Disord*. 2013;19(11):1022-1026.**

Abstract

Aim*:* The first evaluation of the efficacy and safety of ropinirole prolonged release (PR) as an adjunct to L-dopa in Chinese patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa.

Methods*:* In a 24-week, double-blind, placebo-controlled, parallel-group study, subjects with advanced PD were randomized 1:1 to ropinirole PR (N = 175) or placebo (N = 170) as add-on therapy to L-dopa. Primary outcome measure was change from baseline in awake time spent "off". Starting dose of ropinirole PR was 2 mg/day, titrated based on clinical response (maximum 24 mg/day).

Results*:* At week 24, the mean dose of ropinirole PR was 11.4 mg/day with a mean reduction of L-dopa from 506.6 to 411.6 mg/day. Subjects receiving ropinirole PR experienced a significant reduction of "off" time (2.1 h) compared with placebo (0.4 h). Secondary outcome measures including hours of "on" time without troublesome dyskinesis were significantly increased in the ropinirole PR group (1.7 h) compared with placebo (0.3 h). Subjects classified as responders were significantly more frequent in the ropinirole PR (22.8%) than placebo group (2.5%). Efficacy outcomes including Unified Parkinson's disease Rating Scale and PDQ-39 subscales of mobility were significantly improved in the ropinirole PR versus placebo group. The most frequent adverse event experienced in the ropinirole PR group was dyskinesia.

Conclusions*:* This study demonstrated for the first time in Chinese subjects that ropinirole PR improved Parkinson's disease symptoms, permitting a reduction in L-dopa dose. The adverse events observed were consistent with the established safety profile of ropinirole, with no new safety signal identified.