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Month/Year of Review: February 2012
PDL Class: Anti-Parkinson's Agents

Date of Last Review: September 2010
Source Document: Provider Synergies (PS)

Current Preferred Agents:

Anticholinergics:
Benztropine
Trihexyphenidyl HCL

Dopaminergic Agents:
Carbidopa/Levodopa

Dopamine Agonists:
Pramipexole DI-HCL

Combination Product:
Carbidopa/Levodopa/Entacapone

MAO- B Inhibitors:
Selegiline

COMT Inhibitors:
Tolcapone (Tamsar®)

Current Non-Preferred Agents:

Dopaminergic Agents:
Carbidopa/Levodopa ER

MAO-B Inhibitors:
Rasagaline (Azilect®)

COMT Inhibitors:
Entacapone (Comtan®)

Dopamine Agonists*:
Ropinirole (Requip®)
Bromocriptine (Parlodel®)

Abbreviations used:
MAO-B: Monoamine oxidase B, COMT: Catechol-O-methyl transferase
**Amantadine included in antiviral class

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend inclusion of at least one agent from each category with prior authorization (PA) criteria for comparable products

Special Considerations:

- Consider stage of Parkinson's Disease (PD)
- Pramipexole and ropinirole are two drugs specifically approved for restless leg syndrome.

PA Criteria: All non-preferred agents require prior authorization to first try preferred products when feasible for covered diagnosis. Pramipexole and ropinirole require an OHP covered diagnosis for coverage.

Methods

A MEDLINE OVID search was conducted using all treatments for 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 PS 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 Trials:
A total of 79 citations resulted from initial literature search. After inclusion for further review, 18 were evaluated further and five potentially relevant comparative randomized trials were identified through abstract review for appropriate medication, indication, study design, and outcomes (Appendix 1). These trials are briefly described in table 1.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Poewe[1], 2011	Pramipexole ER vs. pramipexole IR	Early PD; monotherapy	Unified Parkinson's Disease Rating Scale	Adjusted mean 33-week UPDRS II+III change: ER -8.2 (-9.5 to -6.9) IR -8.7 (-10.1 to -7.4) Placebo -1.2 (-3.1 to 0.6) • Showing ER was noninferior to IR • Tolerability and safety did not differ between the formulations.
Schapira[2], 2011	Pramipexole ER vs. pramipexole IR	Advanced PD; on levodopa.	Unified Parkinson's Disease Rating Scale	Adjusted mean 18-week UPDRS II+III change: ER -11 (-9.5 to -6.9) IR -12.8 (-10.1 to -7.4) Placebo -6.1 (-3.1 to 0.6)
Stocci[3], 2011	Ropinirole PR vs. ropinirole IR	Advanced PD; adjunctive therapy	Number of patients maintaining a >20% reduction in "off" time	Proportion of patients maintaining 20% reduction in ''off'' time at week 24: PR 66% IR 51% OR 1.82 (95% CI 1.16-2.86) P=0.009 • More withdrawals due to AE in the PR group than IR (12% vs 9%)
Hauser[4], 2010	Pramipexole ER vs. pramipexole IR	Early PD	Unified Parkinson's Disease Rating Scale	Change from baseline to week 18 in UPDRS: ER -8.1 IR -8.4 Placebo -5.1 • Discontinuations due to AE (10.4% ER, 7.8% IR, 4% placebo)
Stocci[5], 2010 STRIDE-PD	Levodopa/carbidopa (Sinemet) vs. levodopa/carbidopa/entacapone (Stalevo)	PD; requiring levodopa initiation	Time to onset of dyskinesia	Discontinuations due to AE: Levo/carb/entacapone: 38 (10.2%) Levo/carb: 24 (6.5%) • Those on levodopa/carbidopa/entacapone had a shorter time to onset and increased frequency of dyskinesia

The STRIDE-PD study evaluated 747 patients with PD over a period of 134 weeks comparing the risk of developing dyskinesia.[5] In this double-blind trial, patients were randomized to levodopa/carbidopa or levodopa/carbidopa/ entacapone (Stalevo®). The primary endpoint was time to onset of dyskinesia. The study found that patients taking levodopa/carbidopa/entacapone had a shorter time to onset of dyskinesia (hazard ratio, 1.29; p=0.04) and increased frequency at week 134 (42% vs. 32%; p=0.02). While not significantly different, time to wearing off and motor scores did trend in favor of the levodopa/carbidopa/ entacapone group. Initiating therapy with added entacapone failed to delay the time of onset or reduce the frequency of dyskinesia compared to levodopa/carbidopa therapy alone.

New drugs:
None

New FDA Indications:
None

New FDA safety alerts:

In August 2010, the FDA notified healthcare professionals about concerns that the use of levodopa/carbidopa/entacapone may be associated with an increased risk of cardiovascular events, including heart attack, stroke, and cardiovascular death, when compared to the use of carbidopa/levodopa.[6] This safety communication is based on findings from the Stalevo Reduction in Dyskinesia Evaluation – Parkinson's disease (STRIDE-PD) trial,[5] which reported an imbalance in the number of myocardial infarctions in patients treated with levodopa/carbidopa/entacapone compared to those receiving only carbidopa/levodopa. At this time, the FDA is reviewing data from a meta-analysis to evaluate the potential cardiovascular risk. In this meta-analysis, of 15 clinical trials comparing Stalevo to carbidopa/levodopa, a small increased risk of cardiovascular events was found in the Stalevo group compared to the carbidopa/levodopa group (27 events versus 10 events, RR 2.46; 95% CI: 1.19-5.09). However, the FDA noted that several factors make these findings difficult to interpret. The clinical trials were not designed to evaluate cardiovascular safety, the majority of patients had preexisting risk factors for cardiovascular disease, and many of the events occurred in one single trial (STRIDE-PD). The FDA continues to assess the results of the STRIDE-PD trial and recommends regularly evaluating the cardiovascular status of patients taking Stalevo, especially if they have a history of cardiovascular disease.

New Systematic Reviews:

Two meta-analyses were identified and were both reviewed by the Centre for Reviews and Dissemination (CRD) and included in the Cochrane database of abstracts of reviews of effects (Appendix 2).[7,8] Both of these relied greatly on indirect comparisons and were recommended by the CRD reviewer to use caution in interpreting the conclusions. A meta-analysis was reported by the Movement Disorder Society and evaluated the comparative benefits and risks of medications used as adjunctive treatment with levodopa in patients with later PD.[8] This review conducted indirect analysis to conclude that dopamine agonist may be more effective than COMT inhibitors or MAO inhibitors when used as adjunctive treatment with levodopa. However, the unknown quality of the trials, lack of information about the studies and the use of indirect comparisons means the authors' conclusions may not be reliable and should be interpreted with some caution.

Evidence-based Clinical Guidelines:

Recommendations based on systematic reviews of best available evidence were published from the Scottish Intercollegiate Guideline Network (SIGN) on the diagnosis and drug management of Parkinson's disease.[9] These have a grade A recommendation to initiate treatment with an agent from the following classes: Dopamine agonists (a non-ergot agonist is preferred to ergot derived agonists), Levodopa with a dopa-

decarboxylase inhibitor, or a monamine oxidase B inhibitor. There is also a grade B recommendation to not use anticholinergic drugs as first line treatment due to the high risk of adverse effects. For treatment advanced disease with motor complications, they recommend adjunct treatment with COMT inhibitors, MAO-B inhibitors, or dopamine agonists to manage motor complications (Grade A). Their recommendation grading scheme relates directly to the strength of the evidence, not the clinical importance of the recommendation.

Rare cases of fatal hepatotoxicity have been reported with use of tolcapone and have led to recommendations of more stringent liver function monitoring. Guidelines from the National Institute for Health and Clinical Excellence (NICE)[10] recommend only using tolcapone after patients have failed therapy with entacapone due to lack of efficacy or side effects. Recommendations from the American Academy of Neurology[11] conclude that entacapone is established as effective in reducing off time, while tolcapone is probably effective and should be used with caution.

Recommendations:

1) Replace tolcapone with entacapone due to reported liver toxicity with tolcapone.
2) Correct PDL to include amantadine as preferred.
3) No further research or review needed.

Appendix 1: Clinical Trial Abstracts:

1. Poewe W, Rascol O, BaroneP, et al. Extended-release pramipexole in early Parkinson disease: a 33-week randomized controlled trial. *Neurology.* Aug 23;77(8):759-66. Epub 2011 Aug 10.

   Objective: To assess the clinical efficacy of a novel once-daily extended-release (ER) formulation of the dopamine agonist pramipexole as monotherapy in patients with early Parkinson disease (PD) and establish its noninferiority vs. standard immediate-release (IR) pramipexole.
   Methods: This was a multicenter, double-blind, parallel study of patients with early PD not receiving levodopa or dopamine agonists, randomly assigned to pramipexole IR, pramipexole ER, or placebo. Seven-week flexible titration was followed by 26-week maintenance, with levodopa permitted as rescue medication. The primary analysis was to test pramipexole ER noninferiority to pramipexole IR based on a change in the Unified Parkinson's Disease Rating Scale (UPDRS) part II+III score at 33 weeks, with noninferiority predefined as a treatment group difference for which the lower bound of the 95% confidence interval (CI) did not exceed -3 points.
   Results: Among 213 ER and 207 IR recipients, the adjusted mean 33-week UPDRS II+III change (excluding levodopa rescue effects) was -8.2 for ER and -8.7 for IR, a difference of -0.5 with a 95% CI of -2.3 to 1.3. Compared with placebo (n = 103), pramipexole ER and pramipexole IR were significantly superior on UPDRS II+III score, all key secondary outcomes, and almost all other endpoints. On the 39-item Parkinson Disease Questionnaire, superiority of pramipexole ER failed to reach statistical significance. Both formulations were equally safe and well-tolerated.
   Conclusion: As monotherapy for early PD, pramipexole ER was noninferior to pramipexole IR and significantly more effective than placebo. Tolerability and safety did not differ between the formulations.

2. Schapira AH, Barone P, Hauser Ra, et al. Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. *Neurology.* 2011 Aug 23;77(8):767-74. Epub 2011 Aug 10.

   Background: In advanced Parkinson disease (PD), immediate-release pramipexole, taken 3 times daily, improves symptoms and quality of life. A once-daily extended-release formulation may be an effective and simple alternative therapy.
   Methods: For a multicenter randomized, double-blind, parallel trial of extended- and immediate-release pramipexole vs. placebo, patients experiencing motor fluctuations while taking levodopa underwent flexible study drug titration and then maintenance at optimized dosage (0.375-4.5 mg/day). The primary endpoint was a change in the Unified Parkinson's Disease Rating Scale (UPDRS) part II+III score at 18 weeks, with further assessments at 33 weeks in a subset of patients. Adverse events were recorded throughout.
   Results: Among 507 patients in the 18-week analyses, UPDRS II+III scores decreased (from baseline means of 40.0-41.7) by an adjusted mean of -11.0 for extended-release pramipexole and -12.8 for immediate-release pramipexole vs. -6.1 for placebo ($p = 0.0001$ and $p < 0.0001$) and off-time decreased (from baseline means of 5.8-6.0 hours/day) by an adjusted mean of -2.1 and -2.5 vs. -1.4 hours/day ($p = 0.0199$ and $p < 0.0001$). Other outcomes were largely corroborative, including a significant improvement in early morning off symptoms. Among 249 pramipexole patients completing 33 weeks, UPDRS II+III and off-time findings showed ≤10.1% change from 18-week values. Both formulations were well-tolerated.
   Conclusion: Extended-release pramipexole significantly improved UPDRS score and off-time compared with placebo, with similar efficacy, tolerability, and safety of immediate-release pramipexole compared with placebo.

3. Stocci F, Giorgi L, Hunter B, Schapira AH. PREPARED: Comparison of prolonged and immediate release ropinirole in advanced Parkinson's disease. *Mov Disord.* 2011 Jun;26(7):1259-65. doi: 10.1002/mds.23498. Epub 2011 Apr 5.

Background: PREPARED was a randomized, parallel-group, double-blind, multicenter study to evaluate the efficacy of adjunctive ropinirole prolonged release (PR) versus immediate release (IR) in patients with advanced Parkinson's disease (PD).
Methods: Patients received once-daily PR (2-24 mg/d; n = 177) or three-times-daily IR (0.75-24 mg/d; n = 173) for 24 weeks. The primary endpoint was the proportion of patients maintaining ≥ 20% reduction from baseline in "off" time over two consecutive visits at Week 24 last observation carried forward (LOCF
Results: At Week 24 LOCF, PR significantly increased the proportion of patients maintaining ≥ 20% reduction in "off" time versus IR (adjusted odds ratio: 1.82; 95% CI: 1.16, 2.86; P = 0.009). Mean (SD) doses at Week 24 LOCF were: PR, 18.6 (6.5) mg/d; IR, 10.4 (6.4) mg/d; mean (SD) reductions from baseline in levodopa (L-dopa) dose were -162 (226) mg and -113 (138) mg, respectively. Adverse events (AEs) were reported by 72% of patients in the PR group and 61% in the IR group; 12% and 9% of patients, respectively, withdrew from the study due to an AE, and 6% and 5%, respectively, reported serious AEs.
Conclusion: Adjunctive PR provided a significantly greater improvement in symptom control in terms of the odds of achieving ≥ 20% maintained reduction in time spent "off" compared with IR. Interpretation may be confounded by the higher doses of PR versus IR that were achieved, in combination with lower doses of L-dopa by the study end. Despite dosing differences, the PR titration regimen was generally well tolerated, with an AE profile similar to that of IR.

4. Hauser RA, Schapira AH, Rascol O, et al. Randomized, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease. *Mov Disord.* 2010 Nov 15;25(15):2542-9.

Background: The objective of this study was to evaluate the efficacy and safety of pramipexole extended release (ER) administered once daily in early Parkinson's disease (PD). Pramipexole immediate release (IR) administered three times daily (TID) is an efficacious and generally well-tolerated treatment for PD. A pramipexole ER formulation is now available.
Methods: We performed a randomized, double-blind, placebo and active comparator-controlled trial in subjects with early PD. The primary efficacy and safety evaluation of pramipexole ER compared with placebo took place at week 18. Two hundred fifty-nine subjects were randomized 2:2:1 to treatment with pramipexole ER once daily, pramipexole IR TID, or placebo.
Results: Levodopa rescue was required by 7 subjects in the placebo group (14%), 3 subjects in the pramipexole ER group (2.9%, P = 0.0160), and 1 subject in the pramipexole IR group (1.0%, P = 0.0017). Adjusted mean [standard error (SE)] change in Unified Parkinson Disease Rating Scale (UPDRS) II [activities of daily living (ADL)] + III (motor) scores from baseline to week 18, including post-levodopa rescue evaluations, was -5.1 (1.3) in the placebo group, -8.1 (1.1) in the pramipexole ER group (P = 0.0282), and -8.4 (1.1) in the pramipexole IR group (P = 0.0153). Adjusted mean (SE) change in UPDRS ADL + motor scores, censoring post-levodopa rescue data, was -2.7 (1.3) in the placebo group, -7.4 (1.1) in the pramipexole ER group (P = 0.0010), and -7.5 (1.1) in the pramipexole IR group (P = 0.0006). Adverse events more common with pramipexole ER than placebo included somnolence, nausea, constipation, and fatigue.
Conclusion: Pramipexole ER administered once daily was demonstrated to be efficacious compared with placebo and provided similar efficacy and tolerability as pramipexole IR administered TID.

5. Stocchi F, Rascol O, Kieburtz K, et al. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. *Ann Neurol*. 2010 Jul;68(1):18-27.

Background: L-dopa is the most widely used and most effective therapy for Parkinson disease (PD), but chronic treatment is associated with motor complications in the majority of patients. It has been hypothesized that providing more continuous delivery of L-dopa to the brain would reduce the risk of motor complications, and that this might be accomplished by combining L-dopa with entacapone, an inhibitor of catechol-O-methyltransferase, to extend its elimination half-life.

Methods: We performed a prospective 134-week double-blind trial comparing the risk of developing dyskinesia in 747 PD patients randomized to initiate L-dopa therapy with L-dopa/carbidopa (LC) or L-dopa/carbidopa/entacapone (LCE), administered 4x daily at 3.5-hour intervals. The primary endpoint was time to onset of dyskinesia.
Results: In comparison to LC, patients receiving LCE had a shorter time to onset of dyskinesia (hazard ratio, 1.29; $p = 0.04$) and increased frequency at week 134 (42% vs. 32%; $p = 0.02$). These effects were more pronounced in patients receiving dopamine agonists at baseline. Time to wearing off and motor scores were not significantly different, but trended in favor of LCE treatment. Patients in the LCE group received greater L-dopa dose equivalents than LC-treated patients ($p < 0.001$).
Conclusion: Initiating L-dopa therapy with LCE failed to delay the time of onset or reduce the frequency of dyskinesia compared to LC. In fact, LCE was associated with a shorter time to onset and increased frequency of dyskinesia compared to LC. These results may reflect that the treatment protocol employed did not provide continuous L-dopa availability and the higher L-dopa dose equivalents in the LCE group.

Appendix 2 : New Systematic Reviews

1. Stowe R, Ives N, Clarke CE, Handley K, Furmston A, et al. Meta-analysis of the comparative efficacy and safety of adjuvant treatment to levodopa in later Parkinson's disease. *Mov Disord*. 2011 Mar;26(4):587-98. doi: 10.1002/mds.23517. Epub 2011 Mar 2.

   Background: Levodopa initially provides good symptomatic control of the symptoms of Parkinson's disease, but motor complications often develop after long-term use. Other classes of antiparkinsonian drugs including dopamine agonists, catechol-O-methyl transferase inhibitors, or monoamine oxidase type B inhibitors are then added as adjuvant therapy. It is unclear whether one class of drug is more effective than another. This meta-analysis evaluates the comparative benefits and risks of these agents as adjuvant treatment in Parkinson's disease patients with motor complications.
   Methods: A systematic review of the literature from 1966 to the end of June 2010 was conducted to identify randomized trials involving a dopamine agonist, catechol-O-methyl transferase inhibitor, or monoamine oxidase type B inhibitor versus placebo, as adjuvant to levodopa therapy.
   Results: Forty-five trials involving nearly 9,000 participants were included. The meta-analysis confirms reports from individual trials that compared with placebo, adjuvant therapy significantly reduces patient off-time and levodopa dose, with improved symptom severity scores (e.g., Unified Parkinson's Disease Rating Scale). However, dyskinesia and numerous other side effects are increased with adjuvant therapy. Few randomized comparisons between drugs have been undertaken, but indirect comparisons suggest that dopamine agonist therapy may be more effective than catechol-O-methyl transferase inhibitor and monoamine oxidase type B inhibitor therapy, which have comparable efficacy. No differences between drugs within each class were observed other than the catechol-O-methyl transferase inhibitor tolcapone appearing more efficacious than entacapone.
   Discussion: This meta-analysis highlights the need for direct head-to-head randomized trials to assess the impact of adjuvant therapy on patient-rated quality of life and health economic outcomes.

2. Kulisevsky J, Pagonabarraga J. Tolerability and safety of ropinirole versus other dopamine agonists and levodopa in the treatment of Parkinson's disease: meta-analysis of randomized controlled trials.

   Background : Dopamine agonists have a well established role in the treatment of Parkinson's disease. The choice of a particular dopamine agonist requires assessing the benefit-risk balance of each available medication.
   Objective: The present study evaluated the tolerability and safety of ropinirole against those of other dopamine agonists (bromocriptine, cabergoline, pramipexole, rotigotine, pergolide) and placebo in monotherapy and adjuvant therapy with levodopa in the treatment of Parkinson's disease, as reported in the peer reviewed medical literature.
   Methods: A systematic review of the medical literature was carried out for relevant English language articles in the MEDLINE database and Cochrane Library from January 1975 to November 2008. The searches were limited to either double-blind clinical trials or randomized clinical trials that included both patients with early Parkinson's disease receiving dopamine agonist monotherapy, and patients at a later stage on combined treatment with levodopa. The Cochrane Collaboration guidelines were followed and the following data were extracted from each study: identifier (title and bibliographical reference), classification of the quality of the evidence (Jadad criteria), type and design of the study, number of patients, patient demographics (average age, sex), Parkinson's disease stage (Hoehn and Yahr Scale), treatment (monotherapy or adjuvant to levodopa), drugs used (including dosage and duration), study objective (safety or tolerability), method of evaluation of results, randomization and blinding, and description of all the adverse events in all treatment groups. A meta-analysis was performed, calculating relative risks (RRs) and confidence intervals for the 12 most relevant adverse events. On the basis of incidence and clinical importance criteria, the final selection of 12 adverse events was made by consensus between the investigators.
   Results: Forty randomized clinical trials were included. Direct comparison of ropinirole with bromocriptine showed a lower RR of constipation for ropinirole (0.55 [95% CI 0.35, 0.89]), while the direct comparison with levodopa showed a lower RR of dyskinesia for ropinirole (0.25 [95% CI 0.09, 0.71]); no significant differences for either dyskinesia or constipation were found when a direct comparison of ropinirole and rotigotine was made. For nausea, ropinirole,

pergolide and rotigotine versus placebo all demonstrated similar RRs (2.25 [95% CI 1.85, 2.74]; 2.28 [95% CI 1.54, 3.37]; and 2.08 [95% CI 1.30, 3.34], respectively). On indirect comparison of ropinirole with pramipexole, ropinirole showed a higher RR for nausea (2.25 [95% CI 1.85, 2.74] vs 1.48 [95% CI 1.24, 1.76]), dizziness (1.87 [95% CI 1.48, 2.37] vs 1.20 [95% CI 1.01, 1.43]), somnolence (2.45 [95% CI 1.30, 4.61] vs 1.68 [95% CI 1.25, 2.25]), and dyskinesia (2.71 [95% CI 1.74, 4.21] vs 2.27 [95% CI 1.58, 3.27]). Pramipexole (3.36 [95% CI 2.41, 4.68], pergolide (4.80 [95% CI 2.24, 10.29]), ropinirole (2.84 [95% CI 1.34, 5.99]), and rotigotine (4.02 [95% CI 1.23, 13.11]) all had a higher RR of hallucinations compared with placebo. Pramipexole also showed a higher RR of confusion (2.64 [95% CI 1.18, 5.91]) and constipation (2.23 [95% CI 1.53, 3.25]) compared with placebo.
Conclusions: In all the included studies, dopamine agonists, including ropinirole, exhibited a higher incidence of adverse events than placebo. Ropinirole showed an adverse event profile similar to other dopamine agonists. Consideration of the clinical characteristics of each patient and the differences in the incidence of adverse events related to each dopamine agonist, may help to optimize the dopamine agonist therapy.

References:

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