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Class Update: Parkinson's Drugs

Month/Year of Review: September 2013
PDL Class: Parkinson's Drugs
Literature Search End Date: July 2013

Date of Last Review: February 2012
Source Document: OSU College of Pharmacy

Current Preferred Agents	Current Non-Preferred Agents
Anticholinergics	
Benztropine tablets	
Trihexyphenidyl tablets/elixir	
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
MAO- B** Inhibitors	
Selegiline capsules	Rasagaline (Azilect®) tablets
Combination Product	
	Carbidopa/Levodopa/Entacapone

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

Previous Recommendations:

- Replace tolcapone with entacapone on the preferred drug list (PDL) due to reported liver toxicity with tolcapone.
- Evidence does not support a difference in efficacy/effectiveness
- Correct PDL to include amantadine as preferred.

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 (RCTs) 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. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New drugs:

None

New FDA Indications:

None

New FDA safety alerts:

None

New Systematic Reviews:

Since the last review, there were two indirect meta-analyses conducted comparing rasagiline with selegiline by Jost WH et. al[4] and rasagiline versus placebo by Minguez-Minguez S et.al.[5](Appendix 3). Both of these relied entirely on indirect comparisons. Due to unknown quality of the trials, lack of information about the studies, the authors' conclusions should be interpreted with some caution.

The analysis by Jost WH et. al. compared the symptomatic efficacy and safety of selegiline vs. rasagiline in both mono- and combination therapy. Six randomized controlled studies on rasagiline and 15 on selegiline were included in the analysis. The analysis used a fixed effects model based on standardized mean differences for efficacy criteria and risk differences of safety outcomes. As outcomes, Unified Parkinson's Disease Rating Scale (UPDRS) (primary) and UPDRS motor functions, mental and Activity of Daily Life (ADL), the Schwab and England scale, the off-time as well as safety as secondary outcomes were used. Rasagiline showed a statistically significant advantage in the primary endpoint of UPDRS total scores (monotherapy: $p = 0.048$, sensitivity analysis: $p = 0.023$; pooled analyses: $p = 0.043$, sensitivity analysis $p = 0.014$) and the secondary endpoint UPDRS motor functions (monotherapy: $p = 0.049$, sensitivity analysis $p = 0.031$; pooled analyses: not significant, sensitivity analysis: $p = 0.046$). For the other secondary outcome parameters, a numerical advantage for rasagiline was found. Discontinuation rates due to adverse effects showed a tendency in favor of rasagiline, but not statistically significant. Risk for adverse events such as

dizziness, hallucinations, diarrhoea and syncope were lower with rasagiline than selegiline (each $p < 0.15$). As there were few trials with combination therapy available, and all had duration of 3 months, analysis of these studies was not conducted. The authors concluded rasagiline showed a statistically significant and clinically relevant advantage over selegiline in the primary endpoint. The superiority of rasagiline was further substantiated with advantages in tolerability and safety.

A Similar analysis by Minguez-Minguez S et.al. compared the efficacy of rasagiline versus placebo for decreasing Parkinson's Disease (PD) symptoms. UPDRS for rasagiline monotherapy and reduction in off-time for combined treatment were the outcomes assessed. Rasagiline monotherapy, in early stages of the disease, reduces the UPDRS score [-3.06 (95% CI -3.81 to -2.31, p<0.00001) with rasagiline 1mg/day]. In combination with levodopa, 1mg/day of rasagiline reduced off-time [-0.93h (95% CI -1.17 to -0.69, p<0.00001)]. However, although rasagiline reduces the UPDRS score [-0.89 (95% CI from -1.78 to 0, p=0.05)] in trials with a delayed-start design, authors found a disagreement between studies and doses, making it difficult to interpret this result. The authors concluded the results confirmed the efficacy of rasagiline in PD, but the clinical significance of these data remained to be established. Furthermore, the delayed-start study design did not establish with certainty the neuroprotective effect of rasagiline.

Guidelines:
National Guideline Clearinghouse (NGC) released treatment guidelines (Appendix 4) on early (uncomplicated) Parkinson's Disease. This guideline is an updated version of the therapeutic management of Parkinson's disease by the joint task force of the European Federation of Neurological Societies and the Movement Disorder Society-European Section.[6] Agents available in the US that carried **level A** recommendation for controlling PD's symptoms including Levodopa IR and CR, pramipexole, ropinirole IR and CR, selegiline and rasagliline. Levodopa also has **level A** recommendation as the most effective symptomatic antiparkinsonian drug, however after a few years of treatment, levodopa is frequently associated with the development of motor complications. As older patients are more sensitive to neuropsychiatric adverse reactions and are less prone to developing motor complications, the early use of levodopa is recommended in the older population (Good Practice Point). The early use of controlled release levodopa formulations is not effective in the prevention of motor complications (**Level A**). The guidelines also included the potential harms associated with each class of drugs. The guidelines recommended gradual discontinuation of anthicholinergics with caution due to abrupt withdrawal may lead to a rebound effect with marked deterioration of parkinsonism. COMT inhibitors increase levodopa bioavailability, so they can increase the incidence of dopaminergic adverse reactions, including nausea, and cardiovascular and neuropsychiatric complications. Side effects such as nausea, vomiting, orthostatic hypotension, confusion, psychosis, and somnolence may occur with administration of any of dopamine agonists and other active dopamine-mimetic medications. Peripheral leg edema is also commonly observed with most agonists. Hallucinations and somnolence are more frequent with some agonists than with levodopa, even in healthy subjects, in the case of somnolence. Side effects such as nausea, vomiting, orthostatic hypotension, confusion, psychosis, and somnolence may occur with administration of any of dopamine agonists and other active dopamine-mimetic medications. Peripheral leg edema is also commonly observed with most agonists. Hallucinations and somnolence are more frequent with some agonists than with levodopa, even in healthy subjects, in the case of somnolence. Impulse-control disorders have recently been identified as a common adverse drug reaction to dopamine agonists. Prevalence ranges between 5% and 15% depending on the author. The principal risk factor is treatment with dopamine agonists, although they can occur on levodopa as well. Personal traits, disturbed decision-making abilities, and younger age have also been implicated. Comorbidities, cognitive impairment, disease severity, and polytherapy are sometimes also mentioned. Up to the present there is no evidence about between-agonists difference in the frequency of these events.

New Trials:

A total of 124 citations resulted from initial literature search. After inclusion for further review, eight were evaluated further and 3 potentially relevant comparative randomized trials were identified through abstract review for appropriate medication, indication, study design, and outcomes (Appendix 4). These trials are briefly described in table 1:

Study	Comparison	Population	Primary Outcome	Results
Mizuno Y et al.[1], 2012	Pramipexole ER (N = 56) vs. pramipexole IR (N= 56)	Patients with modified Hoehn and Yahr stage of 2 to 4; on levodopa.	No predefined primary outcome; secondary outcomes include: unified Parkinson's Disease Rating Scale (UPDRS); percentage of off-time, actual off-time, and percentage of on-time without troublesome dyskinesia during waking hours; and L-dopa daily dose.	UPDRS parts II + III scores decreased significantly from baseline and to a similar degree with pramipexole ER and IR formulations. Both groups reported 83.9% reported adverse events, requiring withdrawal of 3 (5.4%) of ER pts and 2(3.6% IR patients
Chaudhuri R et al.[2], 2012	Ropinirole PR (N = 198) vs. placebo (N = 189)	Advanced PD; on levodopa.	Parkinson's Disease Sleep Scale (PDSS)	Pts with baseline PDSS ≤ 100 showed significant improvement with ropinirole PR vs. placebo in PDSS score from baseline to week 24 last observation carried forward (adjusted mean treatment difference 9.0% (95% CI: 2.76, 15.333; p = 0.0051); not significant in pts with baseline PDSS > 100.
Schapira, A. H. V et al.[3]	Pramipexole ER vs. pramipexole IR	Advanced PD; adjunctive therapy	Unified Parkinson's Disease Rating Scale; daily off-time.	At 32 weeks, the groups showed comparable improvements from DB baseline (pramipexole inception), including, on UPDRS II + III, adjusted mean (SE) changes of −14.8 (1.5) for IR-to-ER and −13.3 (1.6) for ER-to-ER. Rates of premature discontinuation owing to adverse events were 6.5% for IR-to-ER and 4.9% for ER-to-ER.

References:

1. Mizuno Y, Yamamoto M, Kuno S, et al. Efficacy and safety of extended- versus immediate-release pramipexole in Japanese patients with advanced and L-dopa-undertreated Parkinson disease: a double-blind, randomized trial. *Clin Neuropharmacol*. 2012;35(4):174–181. doi:10.1097/WNF.0b013e31825f77b9.

2. Ray Chaudhuri K, Martinez-Martin P, Rolfe KA, et al. Improvements in nocturnal symptoms with ropinirole prolonged release in patients with advanced Parkinson's disease. *European Journal of Neurology*. 2012;19(1):105–113. doi:10.1111/j.1468-1331.2011.03442.x.

3. Schapira AHV, Barone P, Hauser RA, et al. Success rate, efficacy, and safety/tolerability of overnight switching from immediate- to extended-release pramipexole in advanced Parkinson's disease. *European Journal of Neurology*. 2013;20(1):180–187. doi:10.1111/j.1468-1331.2012.03822.x.

4. Jost WH, Friede M, Schnitker J. Indirect meta-analysis of randomised placebo-controlled clinical trials on rasagiline and selegiline in the symptomatic treatment of Parkinson's disease. *Basal Ganglia*. 2012;2(4, Supplement):S17–S26. doi:10.1016/j.baga.2012.05.006.

5. Mínguez-Mínguez S, Solís-García Del Pozo J, Jordán J. Rasagiline in Parkinson's disease: A review based on meta-analysis of clinical data. *Pharmacol Res*. 2013;74C:78–86. doi:10.1016/j.phrs.2013.05.005.

6. National Guideline Clearinghouse | Early (uncomplicated) Parkinson's disease. Available at: http://www.guideline.gov/content.aspx?id=34899. Accessed July 17, 2013.

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

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 Health Resources Commission (HRC).	**Yes:** Inform provider of covered alternatives in class.	**No:** Approve for the shorter of 1 year or length of prescription

Appendix 2

1. **Jost WH, Friede M, Schnitker J. Indirect meta-analysis of randomised placebo-controlled clinical trials on rasagiline and selegiline in the symptomatic treatment of Parkinson's disease. *Basal Ganglia*. 2012;2(4, Supplement):S17–S26.**

Introduction: Selegiline and rasagiline are established in the treatment of Parkinson's disease. As no direct comparative randomised controlled trials on these drugs are available, an indirect meta-analysis was conducted.

Objective: Goal of the meta-analysis was to examine the clinical differentiation between rasagiline and selegiline based on efficacy and safety in Parkinson's disease.

Methods: Literature databases, study registries and references of relevant publications were the basis of our literature search. Studies were selected according to Jadad and Delphi criteria. The analysis used a fixed effects model based on standardised mean differences for efficacy criteria and risk differences of safety outcomes. As outcomes, UPDRS (primary) and UPDRS motor functions, mental and ADL, the Schwab and England scale, the off-time as well as safety as secondary outcomes were used.

Results: Rasagiline showed a statistically significant advantage in the primary endpoint UPDRS total scores (monotherapy: $p = 0.048$, sensitivity analysis: $p = 0.023$; pooled analyses: $p = 0.043$, sensitivity analysis $p = 0.014$) and the secondary endpoint UPDRS motor functions (monotherapy: $p = 0.049$, sensitivity analysis $p = 0.031$; pooled analyses: not significant, sensitivity analysis: $p = 0.046$). For the other secondary outcome parameters, a numerical advantage for rasagiline was found. Discontinuation rates due to adverse effects showed a tendency in favour of rasagiline. Risk for adverse events such as dizziness, hallucinations, diarrhoea and syncope were lower with rasagiline than selegiline (each $p < 0.15$).

Conclusion: This meta-analysis showed a statistically significant and clinically relevant advantage for rasagiline over selegiline in the primary endpoint. The superiority of rasagiline was further substantiated with advantages in tolerability and safety.

2. **Mínguez-Mínguez S, Solís-García Del Pozo J, Jordán J. Rasagiline in Parkinson's disease: A review based on meta-analysis of clinical data. *Pharmacol Res*. 2013;74C:78–86.**

Abstract: Rasagiline (Azilect®) is a selective and irreversible monoamine oxidase B inhibitor, which is well tolerated, safe, improves motor symptoms, and prevents motor complications in Parkinson's disease (PD). Rasagiline is effective in monotherapy and as an adjunct to levodopa-therapy, with beneficial effects on quality-of-life parameters in early and late stages of PD. In this review, we compare the efficacy of rasagiline versus placebo for decreasing PD symptoms. Major databases (Medline, the Cochrane Library) were systematically searched to identify and select clinical randomized control trials of rasagiline. The Unified Parkinson Disease *Rating Scale (UPDRS) for rasagiline monotherapy and reduction in off-time for combined treatment were the outcomes assessed. Rasagiline monotherapy, in early* stages of the disease, reduces the UPDRS score [-3.06 (95% CI -3.81 to -2.31, p<0.00001) with rasagiline 1mg/day]. In combination with levodopa, 1mg/day of rasagiline reduced off-time [-0.93h (95% CI -1.17 to -0.69, p<0.00001)]. However, although rasagiline reduces the UPDRS score [-0.89 (95% CI from -1.78 to 0, p=0.05)] in trials with a delayed-start design, we found a disagreement between studies and doses, making it difficult to interpret this result. In conclusion, our results confirm the efficacy of rasagiline in PD, but the clinical significance of these data remains to be established. Furthermore, the delayed-start study design did not establish with certainty the neuroprotective effect of rasagiline. It is advisable to carry out comparative trials with other drugs used in Parkinson's disease.

Appendix 3

National Guideline Clearinghouse | Early (uncomplicated) Parkinson's disease. February 20, 2012.

Major Recommendations:
The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point [GPP]) are defined at the end of the "Major Recommendations" field.

Early Untreated Patients

The optimal time frame for onset of therapy has not been clearly defined. Once parkinsonian signs start to have an impact on the patient's life, initiation of treatment is recommended. For each patient, the choice between the numerous effective drugs available is based on a subtle combination of subjective and objective factors. These factors include considerations related to the drug (efficacy for symptomatic control of parkinsonism/prevention of motor complications, safety, practicality, costs, etc.), to the patient (symptoms, age, needs, expectations, experience, co-morbidity, socioeconomic level, etc.), and to their environment (drug availability according to national markets in the European Union, variability in economic and health insurance systems, etc.). However, based on the available level of evidence alone, two main issues are usually considered when initiating a symptomatic therapy for early Parkinson's disease (PD): the symptomatic control of parkinsonism, and the prevention of motor complications (see table below).

Currently, there is no uniform proposal across Europe on initiating symptomatic medication for PD. Options include starting treatment with:

- *Monoamine oxidase isoenzyme type B (MAO-B inhibitor)*, like selegiline or rasagiline (**Level A**). The symptomatic effect is more modest than that of levodopa and (probably) dopamine agonists, but they are easy to administer (one dose, once daily, no titration), and well tolerated (especially rasagiline).
- *Amantadine or an anticholinergic* (**Level B**). The impact on symptoms is smaller than that of levodopa. Anticholinergics are poorly tolerated in the elderly and their use is mainly restricted to young patients.
- *Levodopa*, the most effective symptomatic antiparkinsonian drug (**Level A**). After a few years of treatment, levodopa is frequently associated with the development of motor complications. As older patients are more sensitive to neuropsychiatric adverse reactions and are less prone to developing motor complications, the early use of levodopa is recommended in the older population (**GPP**). The early use of controlled release levodopa formulations is not effective in the prevention of motor complications (**Level A**).
- *Orally active dopamine agonist*. Pramipexole, piribedil, and ropinirole immediate- or controlled-release are effective as monotherapy in early PD (**Level A**), with a lower risk of motor complications than levodopa for pramipexole or ropinirole (**Level A**). Older drugs like bromocriptine are supported by lower class evidence, giving a **Level B recommendation**. However, there is no convincing evidence that they are less effective in managing patients with early PD. The benefit of agonists in preventing motor complications (**Level A**, with data up to 5 years only) must be balanced with the smaller effect on symptoms and the greater incidence of hallucinations, impulse-control disorders, somnolence, and leg edema, as compared with levodopa. Patients must be informed of these risks (e.g., excessive daytime somnolence is especially relevant to drivers). Younger patients are more prone to developing levodopa-induced motor complications, and therefore initial treatment with an agonist can be recommended in this population (**GPP**). Ergot derivatives such as pergolide, bromocriptine, and cabergoline are not recommended as first-line medication because of the risk of fibrotic reactions. Rotigotine is administered transdermally using a patch and ropinirole controlled-release (CR) once daily orally, as opposed to the other agonists that are administered orally three times a day. Subcutaneous apomorphine is not appropriate at this stage of the disease. The early combination of low doses of a dopamine agonist with low doses of levodopa is another option, although the benefits of such a combination have not been properly documented.
- *Rehabilitation*. Due to the lack of evidence of the efficacy of physical therapy and speech therapy at the early stage of the disease, a recommendation cannot be made.

Table. Recommendations for the Treatment of Early PD

	Recommendation Level	
Therapeutic Interventions	**Symptomatic Control of Parkinsonism**	**Prevention of Motor Complications**
Levodopa	Effective (**Level A**)	Not applicable
Levodopa controlled release (CR)	Effective (**Level A**)	Ineffective (**Level A**)
Apomorphine	Not used[a]	Not used[a]
Bromocriptine[b]	Effective (**Level B**)	Effective (**Level B**)
Cabergoline[b]	Effective (**Level B**)	Effective (**Level A**)
Dihydroergocryptine[b]	Effective (**Level A**)	No recommendation[c]
Lisuride[b]	Effective (**Level B**)	Effective (**Level C**)
Pergolide[b*]	Effective (**Level A**)	Effective (**Level B**)
Piribedil	Effective (**Level C**)	No recommendation[c]
Pramipexole	Effective (**Level A**)	Effective (**Level A**)
Pramipexole CR[e]	Not available	Not available
Ropinirole	Effective (**Level A**)	Effective (**Level A**)
Ropinirole CR[e]	Effective (**Level A**)	No recommendation[c]
Rotigotine[f]	Effective (**Level A**)	No recommendation[c]
Selegiline	Effective (**Level A**)	Ineffective (**Level A**)
Rasagiline	Effective (**Level A**)	No recommendation[c]
Entacapone[d]	No recommendation[c]	No recommendation[c]
Tolcapone[d]	No recommendation[c]	No recommendation[c]
Amantadine	Effective (**Level B**)	No recommendation[c]
Anticholinergics	Effective (**Level B**)	No recommendation[c]
Rehabilitation	No recommendation[c]	No recommendation[c]
Surgery	Not used	Not used

[a]Subcutaneous apomorphine is not used in early PD.
[b]Pergolide*, bromocriptine, cabergoline and, precautionarily, other ergot derivatives, cannot be recommended as a first-line treatment for early PD because of the risk of valvular heart disorder (Rascol et al., "New concerns," 2004; Rascol et al., "Dopamine agonists," 2004).
[c]No recommendation can be made due to insufficient data .
[d]As catechol-O-methyltransferase (COMT) inhibitors, entacapone and tolcapone should always be given with levodopa. Due to hepatic toxicity, tolcapone is not recommended in early PD.
[e]Controlled-release.
[f]Transdermal patch delivery system.

***Note from the National Guideline Clearinghouse (NGC)**: On March 29, 2007, Permax (pergolide) was withdrawn from the market in the U.S. and worldwide due to safety concerns of an increased risk of cardiovascular events. See the U.S. Food and Drug Administration (FDA) Web site for more information.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of early Parkinson's disease

Potential Harms

- The most commonly reported side effects of *anticholinergics* are blurred vision, urinary retention, nausea, constipation (rarely leading to paralytic ileus), and dry mouth. The incidence of reduced sweating, particularly in those patients on neuroleptics, can lead to fatal heat stroke. Impaired mental function (mainly immediate memory and memory acquisition) and acute confusional state are a well-documented central side effect that resolves after drug withdrawal. The abrupt withdrawal of anticholinergics may lead to a rebound effect with marked deterioration of parkinsonism. Consequently, anticholinergics should be discontinued gradually and with caution.
- As with any dopaminergic drug, *monoamine oxidase isoenzyme type B (MAO-B) inhibitors* can induce a variety of dopaminergic adverse reactions. At the daily doses of selegiline currently recommended, the risk of tyramine-induced hypertension (the 'cheese effect') is low. Concerns that the selegiline/levodopa combination increased mortality rates have been allayed.
- Side effects of *amantadine* are generally mild, most frequently including dizziness, anxiety, impaired coordination and insomnia (>5%), nausea and vomiting (5% to 10%), peripheral distal oedema (unresponsive to diuretics), and headache, nightmares, ataxia, confusion/agitation, drowsiness, constipation/diarrhoea, anorexia, xerostomia, and livedo reticularis (<5%). Less common side effects include psychosis, abnormal thinking, amnesia, slurred speech, hyperkinesia, epileptic seizures (rarely, and at higher doses), hypertension, urinary retention, decreased libido, dyspnoea, rash, and orthostatic hypotension (during chronic administration).
- Catechol-O-methyltransferase (COMT) inhibitors increase levodopa bioavailability, so they can increase the incidence of dopaminergic adverse reactions, including nausea, and cardiovascular and neuropsychiatric complications. Diarrhoea and urine discolouration are the most frequently reported non-dopaminergic adverse reactions.
- Peripheral side effects of *levodopa* include gastrointestinal and cardiovascular dysfunction. Central adverse effects include levodopa motor problems such as fluctuations, dyskinesia and dystonia, and psychiatric side effects such as confusion, hallucinations and sleep disorders. A meta-analysis found approximately 40% likelihood of motor fluctuations and dyskinesias after 4 to 6 years of levodopa therapy. Risk factors are younger age, longer disease duration, and levodopa. In individual studies, the percentage of fluctuations and dyskinesia may range from 10% to 60% of patients at 5 years, and up to 80% to 90% in later years. Neuropsychiatric complications occur in less than 5% of *de novo* patients on levodopa monotherapy.

- Side effects such as nausea, vomiting, orthostatic hypotension, confusion, psychosis, and somnolence may occur with administration of any of *dopamine agonists and other active dopamine-mimetic medications*. Peripheral leg edema is also commonly observed with most agonists. Hallucinations and somnolence are more frequent with some agonists than with levodopa, even in healthy subjects, in the case of somnolence. Though there is no convincing evidence that any agonist is better tolerated than bromocriptine, a recent meta-analysis suggested that while frequencies of somnolence, hallucination, or anxiety cases were higher with non-ergot dopamine agonists (DAs), incidence of vomiting, arterial hypotension, or depression was higher with ergots. The rare but severe risk of pleuropulmonary/retroperitoneal fibrosis is greater with ergot agonists than with non-ergot agonists. The same is true for valvular heart disorders. As pergolide and cabergoline have been the most frequently reported drugs at the present time, they are only used as a second-line alternative option, when other agonists have not provided an adequate response. If employed, regular monitoring of heart valves by ultrasound is mandatory. Impulse-control disorders have recently been identified as a common adverse drug reaction to dopamine agonists. Prevalence ranges between 5% and 15% depending on the author. The principal risk factor is treatment with dopamine agonists, although they can occur on levodopa as well. Personal traits, disturbed decision-making abilities, and younger age have also been implicated. Comorbidities, cognitive impairment, disease severity, and polytherapy are sometimes also mentioned. Up to the present there is no evidence about between-agonists difference in the frequency of these events.

Appendix 4:

1. **Mizuno Y, Yamamoto M, Kuno S, et al. Efficacy and safety of extended- versus immediate-release pramipexole in Japanese patients with advanced and L-dopa-undertreated Parkinson disease: a double-blind, randomized trial. *Clin Neuropharmacol*. 2012;35(4):174–181.**

Abstract

Objectives: To compare the efficacy, safety, tolerability, and trough plasma levels of pramipexole extended-release (ER) and pramipexole immediate-release (IR), and to assess the effects of overnight switching from an IR to an ER formulation, in L-dopa-treated patients with Parkinson disease (PD).

Methods: After a 1- to 4-week screening/enrollment, 112 patients who had exhibited L-dopa-related problems or were receiving suboptimal L-dopa dosage were randomized in double-blind, double-dummy, 1:1 fashion to pramipexole ER once daily or pramipexole IR 2 to 3 times daily for 12 weeks, both titrated to a maximum daily dose of 4.5 mg. Successful completers of double-blind treatment were switched to open-label pramipexole ER, beginning with a 4-week dose-adjustment phase.

Results: Among the double-blind treatment patients (n = 56 in each group), Unified Parkinson's Disease Rating Scale Parts II+III total scores decreased significantly from baseline and to a similar degree with pramipexole ER and IR formulations. In each group, 47 double-blind patients (83.9%) reported adverse events (AEs), requiring withdrawal of 3 ER patients (5.4%) and 2 IR patients (3.6%). Trough plasma levels at steady state (at the same doses and dose-normalized concentrations) were also similar with both formulations. Among open-label treatment patients (n = 53 from IR to ER), 83% were successfully switched (no worsening of PD symptoms) to pramipexole ER.

Conclusions: In L-dopa-treated patients, pramipexole ER and pramipexole IR demonstrated similar efficacy, safety, tolerability, and trough plasma levels. Patients can be safely switched overnight from pramipexole IR to pramipexole ER with no impact on efficacy.

2. **Ray Chaudhuri K, Martinez-Martin P, Rolfe KA, et al. Improvements in nocturnal symptoms with ropinirole prolonged release in patients with advanced Parkinson's disease. *European Journal of Neurology*. 2012;19(1):105–113.**

Background: The 24-week, double-blind Efficacy and Safety Evaluation in PD–Adjunct (EASE-PD Adjunct) study randomized patients with advanced Parkinson's disease (PD) suboptimally controlled with levodopa to once-daily placebo or adjunctive ropinirole prolonged release (2–24 mg/day). We investigated the effect of ropinirole prolonged release on nocturnal symptoms in these patients.

Methods: Total and grouped item PD Sleep Scale (PDSS) scores were analyzed *post hoc* in patients with baseline PDSS total scores ≤100 (troublesome nocturnal symptoms) and >100.

Results: Baseline PDSS total score was ≤100 in 93 of 198 (47%) and 89 of 189 (47%) patients receiving ropinirole prolonged release and placebo, respectively; this subgroup displayed evidence at baseline of greater daily awake 'off' time, reduced night-time sleep and worse quality of life, than the PDSS >100 subgroup. Significant improvements with ropinirole prolonged release versus placebo in PDSS score from baseline to Week 24 last observation carried forward were observed for those with baseline PDSS ≤100 [adjusted mean treatment difference 9.0 (95% CI: 2.76, 15.33; $P = 0.0051$)], but not >100. The PDSS ≤100 subgroup demonstrated treatment benefits for PDSS groupings of motor symptoms on waking and global quality of sleep. Changes in daytime sleepiness were similar between treatment groups. The PDSS >100 subgroup demonstrated significant treatment benefit for global quality of sleep. The unadjusted odds ratio for a positive response with ropinirole prolonged release relative to placebo, for the PDSS ≤100 subgroup, was 2.90 (95% CI: 1.42, 5.95, $P = 0.004$).

Conclusions: Once-daily ropinirole prolonged release improves nocturnal symptoms in patients with advanced PD not optimally controlled with levodopa who suffer troublesome nocturnal disturbance.

3. **Schapira AHV, Barone P, Hauser RA, et al. Success rate, efficacy, and safety/tolerability of overnight switching from immediate- to extended-release pramipexole in advanced Parkinson's disease. *European Journal of Neurology*. 2013;20(1):180–187.**

Background and purpose: For Parkinson's disease (PD), an extended-release (ER) pramipexole formulation taken once daily, has shown efficacy, safety, and tolerability resembling those of immediate-release (IR) pramipexole taken three times daily. The present study assessed, in advanced PD, the success of an overnight switch from adjunctive IR to ER.

Methods: Levodopa users experiencing motor fluctuations were randomized to adjunctive double-blind (DB) placebo, IR, or ER. Amongst completers of ≥18 weeks, ER recipients were kept on DB ER, whilst IR recipients were switched overnight to DB ER at unchanged daily dosage. After a DB week, switch success was assessed. During the next 5 weeks, all patients underwent ER titration to optimal open-label maintenance dosage.

Results: One week post-switch, 86.2% of 123 IR-to-ER and 83.8% of 105 ER-to-ER patients had ≤15% (or ≤3-point, for pre- switch scores ≤20) increase on UPDRS Parts II + III, and 77.9% (of 122) and 70.2% (of 104) had ≤1-h increase in daily OFF- time. At 32 weeks, the groups showed comparable improvements from DB baseline (pramipexole inception), including, on UPDRS II + III, adjusted mean (SE) changes of −14.8 (1.5) for IR-to-ER and −13.3 (1.6) for ER-to-ER. Rates of premature discontinuation owing to adverse events were 6.5% for IR-to-ER and 4.9% for ER-to-ER.

Conclusions: By OFF-time and UPDRS criteria, majorities of patients with advanced PD were successfully switched overnight from pramipexole IR to ER at unchanged daily dosage. During subsequent maintenance, pramipexole showed sustained efficacy, safety, and tolerability, regardless of formulation (IR or ER) in the preceding DB trial.