VA/DoD Drug Class Review: Dopamine Agonists

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Introduction

The purpose of this review is to evaluate whether the dopamine agonists (DA) are therapeutically interchangeable.

The dopamine agonists are subcategorized as ergoline and non-ergoline. The ergoline compounds (bromocriptine and pergolide) are derived from the ergot alkaloids. The non-ergoline compounds include pramipexole and ropinirole. Though the exact mechanism of action in Parkinsonism is unknown, all of the dopamine agonists are thought to work by directly stimulating postsynaptic dopaminergic receptors in the nigrostriatal system.

The two ergoline agents were introduced into the market in the 1980's. Only bromocriptine, which was FDA-approved prior to January 1, 1982, is available in generic form.

Table 1: Dopamine agonists available in the U.S for the treatment of Parkinson's disease

Generic	Brand (Manufacturer)	Strengths & formulations	FDA approval date
Bromocriptine	Parlodel (Novartis); Generics available	Tablets 2.5, and 5 mg	N/A*
Pergolide	Permax (Amarin) Generics available**	Tablets 0.05, 0.25, and 1 mg	12/30/88
Pramipexole	Mirapex (Pharmacia)	Tablets 0.125, 0.25, 0.5, 1, and 1.5 mg	7/1/97
Ropinirole	Requip (SKB)	Tablets 0.25, 0.5, 1, 2, 3, 4 and 5 mg	9/19/97

*Parlodel was approved prior to Jan 1, 1982.

** pergolide was voluntarily withdrawn from the market on March 29, 2007

Parkinson's Disease is a degenerative brain disorder that affects approximately 500,000 to 1 million people in the United States. Approximately 50,000 new cases are diagnosed each year. The Department of Veterans Affairs' Parkinson's Disease Research Education and Clinical Centers (PADRECC) estimates that 40,000 veterans are treated annually for the disorder. The number of patients under treatment in the DoD Health System is estimated to be around 23,000.

The average age of onset is 58 years, however the disease follows no age limits. Development of symptoms has occurred in patients as young as twenty and as old as ninety years. Symptoms of this disease include resting tremor, muscle rigidity, bradykinesia, and postural instability. The underlying etiology of Parkinson's disease involves the progressive loss of dopamine producing cells in the substantia nigra, which results in a decrease in dopamine in the corpus striatum. As the disease progresses, patients develop worsening symptoms and co-morbidities. Additionally, a quality of life becomes more adversely affected with disease progression. The goal of therapy is to ameliorate the lack of dopamine within the substantia nigra. This can be accomplished through the use of DAs and/or levodopa. Additionally, the concept of neuroprotective agents is also being investigated. The major disadvantage for levodopa is that the effectiveness of this medication deteriorates over time. This phenomenon of loss of effect occurs with most of the medications used in PD treatment. Patients may witness a decreased response to levodopa therapy within 5 years after initiation of therapy.

In 2002, an update to the American Academy of Neurology's *Practice Parameter for the Initiation of Treatment for Parkinson's Disease* was published. One of the conclusions of this update was that the DA may be considered for first-line use in selected patients. DA are no longer viewed as solely levodopa sparing but are now used for their potential neuroprotective effects and to delay the initiation of levodopa therapy. The other major use of DA involves the treatment or prevention of dyskinesias and motor fluctuations associated with levodopa therapy. Dyskinesias are thought to be due to hypersensitivity of the dopamine receptors. This is likely secondary to the fluctuation in receptor stimulation as a result of variations in blood/brain levels of drug. The motor fluctuations consist of periods of good mobility and motor function ("on") alternating with periods of impaired motor function ("off"). As the duration of the patient's response to medication becomes shorter and shorter ("wearing off"), they begin to have unpredictable fluctuations known as the "on-off" phenomenon. This results from the levels of drug which can induce dyskinesias may be low or lower than that needed to alleviate PD symptoms. The shortening of the response time eventually blurs the therapeutic range of the levodopa into the toxic range. When used as an adjunct to levodopa, DA can be used in a lower dose and effectively decrease the involuntary movements secondary to the higher doses while lengthening the time before the overlap of the therapeutic and toxic ranges of levodopa. When used as monotherapy, the DAs can delay the need to use levodopa, though most patients will eventually require levodopa.

FDA-Approved Indications and Off-Label Uses

FDA-approved indications & prominent off-label uses are shown below.

Table 2: FDA-approved indications

	Drug			
Indication	**Bromocriptine (Parlodel)**	**Pergolide (Permax)**	**Pramipexole (Mirapex)**	**Ropinirole (Requip)**
Treatment of idiopathic or post-encephalitic Parkinson's disease	X			
Adjunctive treatment to levodopa/ carbidopa in the management of signs and symptoms of Parkinson's disease		X		
Treatment of signs and symptoms of idiopathic Parkinson's disease			X	X
Hyperprolactinemia with associated dysfunctions, including amenorrhea, galactorrhea, infertility or hypogonadism	X			
moderate to severe primary RLS			X	X
Acromegaly	X			

Off label uses:

Bromocriptine: Neuroleptic-malignant syndrome

Pergolide: Hyperprolactinemia, restless legs syndrome, nocturnal myoclonus, Tourette's syndrome, chronic motor or vocal tic disorder

Methods

The methodology of this review is described below:

1) **Included drugs:** This review includes the following DA drugs for the treatment of Parkinson's disease: bromocriptine, pergolide, pramipexole, and ropinirole. Apomorphine, an injectable dopamine agonist, has recently been approved for "rescue" use in patients with intractable "off" periods. At this time, this represents the entire class of DAs FDA-approved for treating Parkinsonism. No other agents are nearing FDA approval.

Since apomorphine is only used for rescue and utilizes the subcutaneous injection route,, it was excluded from this review.

2) **Literature search:** We conducted a search of the literature via electronic databases. This search included the entire Evidence Based Medicine Controlled Trials database in OVID® (no date restrictions) and MEDLINE from 1996 to present. A detailed search strategy is included in appendix A.

Pharmacology

The DA directly stimulate central and peripheral dopamine receptors. They exert their anti-Parkinson effect by stimulating the post-synaptic dopamine receptors in the nigrostriatal system. Pramipexole and ropinirole have been shown to have intrinsic activity at the D_2 and D_3 receptor subtypes. However, the relevance of D_3 receptor binding in Parkinson's disease is unknown. Ropinirole has moderate *in vitro* affinity for opioid receptors. There is evidence that the DAs also act as neuroprotective agents by reducing the turnover and release of free-radical metabolites of dopamine, thereby reducing oxidative stress.

Bromocriptine, an ergoline DA, also reduces prolactin levels in patients with physiologically elevated prolactin by stimulating the dopaminergic neurons in the tuberoinfundibular process. Pergolide, the other ergotamine derived compound, has been studied for use in hyperprolactinemia but is not FDA-approved for this indication.

Bromocriptine also produces a prompt and sustained reduction in circulating levels of growth hormone (GH) in patients with acromegaly. This reduction in GH is thought to be achieved via stimulation of dopaminergic neurons in the hypothalamic-pituitary axis.

Pharmacokinetics

Table 3 lists the pharmacokinetic properties of the DAs.

Table 3: Pharmacokinetic properties

Drug	Tmax (hr)	Estimated half-life (hr)*	Plasma protein binding	Bioavailability	Kinetics	Route of Excretion	Metabolism via CYP450 isoenzyme
Bromocriptine	1-1.5	45	90%	28%	Linear	Bile	None
Pergolide	1-2	15-42	90%	60%*	Unknown	Renal	None
Pramipexole	2	8-12	15%	90%	Linear	Renal	None
Ropinirole	1-2	6	30-40%	55%	Linear	Hepatic	1A2 (extensive)

*Estimated, based on recovery studies.

Dosing and Administration

All of the DAs listed above are available as orally administered, non-sustained release tablets.

In the treatment of Parkinson's disease, doses of all the DAs must be individually titrated for each patient. In the clinical trials of pramipexole and ropinirole, dosage was initiated at subtherapeutic levels to avoid intolerable adverse effects. Dosing is recommended to begin at these low subtherapeutic levels, with gradual titration to achieve a maximum therapeutic effect, balanced against the principal side effects of dyskinesia, somnolence, dry mouth, hallucinations (pramipexole), and dizziness (ropinirole).

Special populations – Because pramipexole is eliminated through the kidneys, the dosage of pramipexole must be adjusted in renal insufficiency. This is a characteristic not shared with the other DAs.

Table 4: Dosing and administration

	Bromocriptine	Pergolide	Pramipexole	Ropinirole
Initial Dose	1.25 mg bid with meals	0.05 mg qd for 1st two days	0.125 mg tid x 1 week	0.25 mg tid x 1 week
Recommended Titration	Assess at 2-week intervals, may increase by 2.5mg/day every 14-28 days	Gradually increase by 0.1 or 0.15 mg q 3rd day for next twelve days of therapy. Then increase by 0.25 mg/day every 3rd day until therapeutic dosage achieved	Week 2 – 0.25 mg tid Week 3 – 0.5 mg tid Week 4 – 0.75 mg tid Week 5 – 1.0 mg tid Week 6 – 1.25 mg tid Week 7 – 1.5 mg tid	Week 2 – 0.5 mg tid Week 3 – 0.75 mg tid Week 4 – 1.0 mg tid After week 4, if necessary increase by 1.5 mg/day each week up to 9 mg/day, then by 3 mg/day weekly up to a total daily dose of 24 mg/day
Dose – Response Relationship / Maximum Dose	Maximum dose = 100 mg/day	Efficacy at doses above 5mg/day has not been evaluated	Normal maintenance dose is maximal at 4.5 mg/day	Maximum dose = 24 mg/day.
Food Considerations	Recommended to be taken with food	May be taken without regard to food	Does not affect the extent of absorption, however Tmax is increased by 1 hour when given with a meal	Does not affect the extent of absorption, however Tmax is increased by 2.5 hour when given with a meal. May be taken without regard to food
Dose adjustments in special populations	N/A	N/A	Renal insufficiency Mild: start 0.125 mg tid, max 1.5 mg tid. Moderate: start 0.125 mg bid, max 1.5mg bid Severe: start 0.125 mg qd, max 1.5 mg qd	Titrate with caution in patients with hepatic impairment

Efficacy

Studies with the DAs date back at least as far as 1975. Since 1) all four drugs have been shown to be more efficacious than placebo, 2) all have been studied with and against levodopa, plus 3) pergolide, pramipexole and ropinirole have been studied against bromocriptine, the use of evidence based reviews were deemed sufficient for the bulk of evaluation.. The evidence based reviews of the DA published in *Movement Disorders* and *Cochrane Systematic Reviews* are included in this evaluation.

Efficacy Measures

There is still no uniformly agreed upon outcome variable for measuring disease progression. However, most researchers use The Unified Parkinson's Disease Rating Scale (UPDRS), a rating tool designed to follow the longitudinal course of Parkinson's disease and assess response to therapy. Many neurologists find it too cumbersome to use in clinic. It can also be used to help determine when patients' symptoms are problematic enough to require pharmacologic treatment. Treatment with either levodopa or the DA's can result in improvement on the UPDRS score. The entire scale can be viewed at http://www.wemove.org/par_rs.html and has been in use since 1987. A total of 199 points are possible with 0 representing no disability and 199 representing total disability. The scale is divided into six sections as follows:

I. Mentation, Behavior and Mood

Comment [r1]: From: C. Warren Olanow, MD, FRCPC; Ray L. Watts, MD; and William C. Koller, MD, PhD. An algorithm (decision tree) for the management of Parkinson's disease (2001): Treatment Guidelines. Neurology 2001;56(Suppl 5):S1-S88.

Comment [r2]: Fahn S, Elton R, Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information 1987, pp 15 3-163, 293-304.

II. Activities of daily living (ADLs) taking both "on" and "off" symptoms into account

III. Motor Examination

IV. Complications of Therapy (In the past week) Complications are divided into:

a. dyskinesias,

b. clinical fluctuations

c. Other complications

V. Modified Hoehn and Yahr Staging

VI. Schwab and England Activities of Daily Living Scale

The last two sections of UPDRS are qualitative rating scales that were in use prior to UPDRS and have been incorporated into the UPDRS. They are described at the aforementioned website. UPDRS is an attempt to quantitate response to therapy and disease progression.

Efficacy Trials

Parkinson's Disease

Evidence for the efficacy of the DAs comes from several well designed randomized controlled trials. These were thoroughly studied in the Cochrane Reviews. These reviews looked at: pergolide vs. placebo (2 studies, 488 patients); pramipexole vs. placebo (4 studies, 669 patients); and ropinirole vs. placebo (4 studies, 502 patients). The reviewers concluded that pergolide, pramipexole and ropinirole were statistically significantly better than placebo. Cochrane reviews were also conducted to study: pergolide vs. bromocriptine vs. levodopa (3 studies, 348 patients); pramipexole vs. bromocriptine (1 study, 246 patients); and ropinirole vs. bromocriptine (3 studies, 888 patients). The reviewers came to the following conclusions. 1) Pergolide comparative trials: different rating scales were used for each study. Cannot combine efficacy results in a quantitative manner. 2) Pramipexole comparisons: The study was not powered to examine differences between active treatment arms. However, both pramipexole and bromocriptine were significantly better than placebo. 3) Ropinirole comparisons: There was no statistical difference between ropinirole and bromocriptine. The results of efficacy trials are presented in Appendix B.

Restless leg syndrome

Evidence for the use of DA in restless leg syndrome (RLS) has been based mostly on case reports, case series and very small clinical trials. They have become the preferred agent over levodopa due to the complications associated with that therapy. The majority of reports and/or trials include subjective measures of symptomatic relief as assessed by patient interview or questionnaire, as well as objective sleep testing which measures periodic leg movements of sleep (PLM), REM sleep rating and number of arousals due to PLM. In summary, the DA bromocriptine, pergolide, pramipexole and ropinirole have all been shown efficacious in the treatment of RLS. There have been no comparative trials between the DA therefore no agent can be considered superior to the others. Becker, et al conducted a trial of bromocriptine versus levodopa, demonstrating equipotency of the DA to levodopa. Specifics of the trials can be found in Appendix C.

Cost Effectiveness Studies

There are few articles in the medical literature looking at the cost-effectiveness of dopamine agonists. Hoerger, et al (1998) evaluated the cost-effectiveness of pramipexole in comparison to levodopa alone or pramipexole plus levodopa in a multi-stage mathematical model of the hypothetical treatment of patients with early stage and advanced Parkinson's Disease. The primary outcome measures were total direct and indirect costs and quality adjusted life years (QALYs). They found that pramipexole had higher costs but was more effective than baseline treatments. For patients with early onset PD, the incremental CE ratio for pramipexole was $8837/QALY. For advanced PD, the incremental CE ratio was $12,294/QALY. These ratios were lower than the incremental CE ratios of many widely used medical interventions, meaning that pramipexole is a cost-effective choice for the treatment of PD in comparison to levodopa alone. The authors did not initially include pergolide or bromocriptine in the model. However, they included them in sensitivity analyses, and the results show that pramipexole is more effective and

less costly than bromocriptine plus levodopa. The combination of pergolide plus levodopa was more costly and only slightly more effective than regimens including pramipexole. The authors warn that the resulting incremental CE ratio ($908,308) must be viewed cautiously because of the very small difference in the effectiveness of the competing regimens. A major limitation of this model is that the data used to estimate non-drug health care resource use and cost is based on a survey of ambulatory outpatients in a single state, raising questions of how representative the model is for the entire U.S. PD population.

Shimbo, et al (2001) developed a Markov model that evaluated the cost-effectiveness of three treatments (levodopa, levodopa plus bromocriptine, and levodopa plus pergolide) over a 10 year time horizon. The primary outcome measures were direct health care costs and QALYs, and the model takes the societal perspective. The model uses transition probabilities to evaluate the costs and QALYs associated with progression of a population through HY stages 1 to 5. Its results show that the incremental cost-effectiveness of dopamine agonists was $172,300 to $178,900 for HY stage 2 patients. When started in HY stage 3 to 5, DA's are less costly and more effective (dominant) compared to levodopa. Generic bromocriptine was dominant even in HY stage 2. When l-dopa + bromocriptine was compared to l-dopa + pergolide, the incremental cost effectiveness of the pergolide combination was $480,000/QALY in stage 2, $130,000/QALY in stage 3. Generic bromocriptine appears to be more cost-effective than levodopa alone or in combination with pergolide. However, if brand name bromocriptine used, pergolide is more cost-effective.

Davey, et al (2001) developed a decision analytic model to assess the cost-effectiveness of pergolide versus bromocriptine in the treatment of PD. The model ran for 20 cycles of 6 month's duration, and the patients progress through six stages: Hoen-Yahr stages 1-5 and death. The outcome measure was cost per life-year in HY stage 1-3. The results showed that cost savings with pergolide under various scenarios ranged from $68 to $2,782 for the entire period. Pergolide was found to be less costly and more effective than bromocriptine in all scenarios, with an overall average savings of $1,076 and a gain of 0.044 life years in HY stages 1-3. Major limitations of this analysis are: 1) Cost data was based on expert opinion from a survey of only six physicians. 2) Treatment duration was assumed to be only 6 months, while benefits of pergolide were assumed to last from 6 months to 10 years following treatment. This extrapolation may not be realistic given the natural course of PD. 3) Patients in the pergolide group were assumed to enter treatment with lower HY scores.

Two of the analyses conclude that the studied dopamine agonists are cost-effective in early or late stage PD when compared to levodopa alone. While it may be tempting to make inferences about the relative cost effectiveness among the dopamine agonists based on these studies, it may not be appropriate do so. The methodologies (assumptions, model type, cost estimating) differ between the three studies, making a comparison of the results across studies invalid. Additionally, methodology issues within the studies raise concerns that the differences estimated might not be firmly established. Finally, the relatively small differences in effectiveness seen in the Hoerger and Davey studies may not be clinically meaningful. For example a gain of 0.044 life years in HY stages 1-3 (Daley) is equivalent to approximately 15 days in a 10-year treatment model.

Quality of Life Studies

No formal quality of life studies were found in the literature. However, a few clinical trials looked at quality of life as a secondary outcome measure. Generally, the results of these trials were as expected: patients receiving a DA alone or in conjunction with levodopa scored higher on quality of life than patients receiving placebo treatment.

In the most extensive of these studies, Guttman and members of the International Pramipexole Study Group looked at pramipexole and bromocriptine versus placebo in the treatment of advanced Parkinson's disease. Quality of life assessments showed significant differences (improvement) in both of the active treatment groups compared with controls with respect to the FSQ (Functional Status Questionnaire) Basic Activities of Daily Living, Intermediate Activities of Daily Living, and Mental Health Scales. Other measurements that were part of the FSQ, such as days in bed due to illness, approached statistical significance (p=0.054) but did not show any differences between bromocriptine and pramipexole. The researchers also looked at scores using the European Quality of Life (EurQol, EQ-5D) instrument. This instrument is a utility-valued questionnaire. EurQol testing approached statistical

significance (p=0.065), with subgroup analysis showing that pramipexole produced significantly better quality of life than controls (=0.02) but bromocriptine did not (p=0.26). This trend was the only quality-of-life measurement that showed that pramipexole produced statistically significant improvements in quality of life compared to bromocriptine.

Likewise, Koller et al studied pergolide versus tolcapone an inhibitor of catecholamine O-methyl transferase (COMT), as add-on to levodopa therapy in Parkinson's disease patients with motor fluctuations. The Parkinson's disease questionnaire (PDQ)-39 was used to measure health related quality of life. Both pergolide and tolcapone were able to produce a clinically meaningful change in PDQ-39 scores, at –8.7 and –14.2 respectively. However, there was a statistically significant difference ($p<0.05$) in lowering of PDQ scores between pergolide and tolcapone, with tolcapone providing greater improvement in quality of life.

Safety /Tolerability

Serious Adverse Events

Potential for inflammation, fibrosis and cardiac valvulopathy with pergolide - There have been rare reports of pleuritis, pleural effusion, pleural fibrosis, pericarditis, pericardial effusion, and cardiac valvulopathy involving one or more valves, and retroperitoneal fibrosis in patients taking pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of the drug. Pergolide should be used with caution in patients with a history of these conditions, particularly those patients who experienced the events while taking ergot derivatives.

Retroperitoneal fibrosis – Retroperitoneal fibrosis has also been reported in a few patients receiving long-term therapy (2-10 years) with bromocriptine mesylate in doses ranging from 30-140 mg daily.

Required Monitoring

Because of the potential for cardiac valvulopathy mentioned above, it is recommended that patients prescribed pergolide be evaluated at baseline and monitored periodically with appropriate radiographic and laboratory studies during therapy. Because of the potential need for dosage adjustment, clinicians should monitor the renal functioning of patients prescribed pramipexole and the hepatic functioning of patients prescribed ropinirole.

Table 5 Monitoring requirements

	Bromocriptine	Pergolide	Pramipexole	Ropinirole
At baseline	N/A	Cardiac	N/A	N/A
During therapy	N/A	Cardiac	Renal	Hepatic
After discontinuation of therapy	N/A	N/A	N/A	N/A

Side Effect Profile

General Comments – The most common serious side effects seen with the DAs are nausea, dizziness, somnolence, hallucinations, confusion/disorders of thinking, vision abnormalities and hypotension.

The incidence of vision abnormalities and hypotension is fairly low, ranging from 2 to 6% for both side effects in all of the DAs. The incidence of dizziness, hallucinations, confusion/disorders of thinking, and somnolence is somewhat higher (see table below), and these side effects have been reported to be more problematic. Somnolence, in particular, has been reported to occur without warning in patients taking ropinirole and pramipexole, prompting warnings about "falling asleep during activities of daily living" to appear in their FDA approved labeling.

"Unintended sleep episodes" have been reported in some patients receiving treatment with DAs and levodopa. Other terms used in the literature include "falling asleep during activities of daily living", "sudden-onset sleep (SOS)", and "sleep attacks". It has been suggested that the term "sleep attack" implies that the events are inevitable and occur without warning. However, some clinical experts believe that unintended sleep episodes always occur in the setting of pre-existing somnolence (i.e., there is a warning of sleepiness, rather than occurring suddenly and unpredictably) although patients may not give such a history. Therefore, these clinician prefer to use the term "unintended sleep episodes" which implies that at-risk individuals can be identified and the episodes prevented by instituting appropriate treatment measures.

Although the exact mechanism is unknown, it is theorized that unintended sleep episodes may represent an extreme form of sedation and result from a number of factors including excessive daytime sleepiness and the sedating effects of dopaminergic therapies. However, controlled trials are needed to confirm this theory. Factors predicting unintended sleep episodes, as well as effective prevention and treatment strategies have yet to be determined.

The prevalence of unintended sleep episodes has been reported to be 6.6% and has been seen in all of the dopaminergics used to treat Parkinsonism. This estimate is based on a systematic review by Homann, et al. The reviewers studied reports of sleep attacks or narcoleptic-like attack in patients with Parkinson's disease published between July 1999 and May 2001. They found reports of unintended sleep episodes in 124 patients in 20 published trials. The total number of evaluable patients in the trials numbered 1878.

Table 6: Unintended sleep episodes as reported in Homann et al. (n = 124 patients)

Drug	Ropinirole	Pramipexole	Lisuride* or piribedil*	Bromocriptine	Levodopa monotherapy	Pergolide	Apomorphine	Cabergoline*
Patients (%)	38 (30.6)	32 (25.8)	23 (18.6)	13 (10.5)	8 (6.4)	5 (4.0)	2 (1.6)	1 (0.8)

* Not available in the U.S. for the treatment of Parkinson's disease.

While all of the dopaminergics were represented, over half of the reported events involved pramipexole or ropinirole. The reviewers also concluded that there was not a correlation between the likelihood of an unintended sleep episode and dopaminergic drug dosage, treatment duration, or the presence or absence of preceding signs of tiredness. The publications revealed no treatment strategy that consistently prevented unintended sleep episodes.

Hobson, et al, reported a survey conducted by a Canadian Movement Disorders Group suggests that the use of the Epworth Sleepiness Scale may provide appropriate sensitivity in determining past episodes of falling asleep while driving. However, it is unknown if this method can reliably predicate future instances.

Safety Studies – There are few well-designed RCTs looking specifically at safety of the DAs in the treatment of Parkinsonism. One well-designed meta-analysis by Etminan, Gill, and Samii compared the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease.

In this study, the reviewers examined 13 randomized controlled trials to determine if there were quantifiable differences in risk for adverse effects (including dizziness, nausea, hypotension, hallucinations, and somnolence) between pramipexole and ropinirole. The reviewers conducted two separate analyses in order to quantify the differences when compared to levodopa and when compared to placebo. The first analysis consisted of four studies with pramipexole compared with levodopa and three studies of ropinirole compared with levodopa and involved a total of 1059 patients. The second analysis used placebo as the comparator against pramipexole in three studies and ropinirole in three studies.

Dizziness, nausea and hypotension - Compared with levodopa, the pooled relative risk (RR) for pramipexole and ropinirole causing dizziness was 0.96 (95% CI 0.61-1.51). The RR for nausea was 1.13 (95% CI 0.92-1.39), and the RR for hypotension was 1.01 (95% CI 0.67-1.51). There was no statistically significant difference in the risk of dizziness, nausea and hypotension with either pramipexole or ropinirole when compared to levodopa.

The pooled RR (pramipexole and ropinirole combined) of hypotension compared with placebo was 2.14% (95% CI 1.02-4.48). The risk of hypotension was approximately four times higher with ropinirole than with pramipexole when each drug was individually compared to placebo (6.46, 95% CI 1.47-28.28) vs 1.65 (95% CI 0.88-3.08).

Somnolence - The pooled RR for pramipexole and ropinirole combined vs. levodopa for somnolence was 1.61 (95% CI 1.21-2.13). There was no significant difference between the drugs when compared individually with levodopa. When compared with placebo, the pooled RR for somnolence was 3.16 (95% CI 1.62-6.13). Compared individually with placebo, the risk of somnolence was 2.01 (95% CI 2.17-3.16) with pramipexole and 5.72 (95% CI 2.34-14.01) with ropinirole.

Hallucinations - The pooled RR of hallucinations was 1.92 (95% CI 1.08-3.43) when compared with levodopa. There was no significant difference in the risk of hallucinations between the two drugs when each was compared individually to levodopa. Compared with placebo, the pooled RR for hallucinations was 4.24 (95% CI 1.97-9.62). The RR with pramipexole was 5.2 (95% CI 1.97-13.72), and the RR with ropinirole was 2.75 (95% CI 0.55-13.73).

The results of the meta-analysis suggest that the risks of dizziness, nausea, and hypotension are not increased with either pramipexole or ropinirole when compared with levodopa. However, the risks for somnolence and hallucinations are increased when compared to levodopa, and increased further compared to placebo. Although there appears to be a trend towards increased somnolence with ropinirole compared to pramipexole, and a trend towards increased hallucinations with pramipexole compared to ropinirole, one cannot unequivocally state that these differences exist because of the overlapping 95% confidence intervals in the results.

Summary - Side effects caused by DAs are similar to those of levodopa, including nausea, vomiting, orthostatic hypotension, confusion, and hallucinations. These effects can usually be avoided by initiating treatment with very small doses and titrating to therapeutic levels slowly over several weeks. Patients intolerant of one agonist may tolerate another. In addition to slow titration, nausea may potentially be avoided by having the patient take the medication with food. As is seen with all of the antiparkinsonian drugs, elderly and demented patients are much more susceptible to psychiatric side effects.

Ergot-related side effects such as Raynaud's phenomenon, erythromelalgia, and retroperitoneal or pulmonary fibrosis are uncommon with bromocriptine and pergolide, and do not occur at all with the nonergot agonists ropinirole and pramipexole. In epidemiologic studies looking at pergolide, the onset of pulmonary and/or retroperitoneal fibrosis has been found to occur an average of 2 years following the initiation of therapy. Cardiac evaluations (e.g. Echocardiogram) should be conducted periodically on all patients taking ergot DA to monitor for the development of valve abnormalities.

Dopamine receptor agonists decrease prolactin concentration. Thus, there is a potential for decreased milk production in postpartum women taking these agents. However, this is not generally considered problematic because these agents are contraindicated in women who are breast-feeding.

Table 7 below summarizes ADR information for the DAs. The data are from pooled clinical trial data from package inserts and include all adverse reactions reported at a rate of least 1% and > placebo.

Table 7: Treatment-emergent adverse events

	Bromocriptine	Pergolide	Pramipexole	Ropinirole
Insomnia (%)		8%	17%	
Somnolence (%)	3%	10%	22%	40%
Anorexia (%)	4%	4.8%	4%	4%
Constipation (%)	14%	10.6%	14%	6%*
Dysphagia (%)			2%	2%*
Nausea (%)	18%	24%	28%	60%
Vomiting (%)	2%	3%		12%
Asthenia (%)			14%	6%
Dizziness (%)	17%	14%	25%	40%
Abdominal pain (%)				6%
Hallucinations (%)		11.6%	9%	5%
Rhinitis (%)	4%	12%	3%*	4%

	Bromocriptine	Pergolide	Pramipexole	Ropinirole
Confusion (%)	>1%	11%	4%	5%
Orthostatic hypotension (%)	6%	2%	2.3%	2%
Vision Abnormalities (%)		5%	2%	6%
Peripheral edema (%)			5%	7%

* Studies included patients on combination therapy with levodopa or carbidopa/levodopa

Special Populations

Elderly - Parkinson's disease is predominantly a disease of the middle-aged to elderly. DAs have been extensively studied in elderly Parkinson patients, with no safety problems emerging. In practice, dosage of the DAs is individually titrated to achieve a maximum therapeutic effect, balanced against the principal side effects seen with DAs. Therefore, there is generally no dosage adjustment required for use in the elderly.

Pregnancy - The ergoline DAs are also used in women of childbearing age for hyperprolactinemia and post-partum breast engorgement. There is a specific warning against the use of bromocriptine in pregnancy. There is a potential for hypertensive disorders of pregnancy (eclampsia, preeclampsia, or pregnancy-induced hypertension) when taking bromocriptine and the benefits must be weighed against the risks. In all circumstances, the drug should be withdrawn if a pregnant patient experiences any of the above-mentioned disorders.

Renal insufficiency – It is recommended that the dosage of pramipexole be adjusted in patients with moderate or severe renal insufficiency (see table on dosing & administration).

Table 8: Use in special populations

	Bromocriptine	Pergolide	Pramipexole	Ropinirole
Contraindications	Uncontrolled hypertension, hyperprolactinemia patients who become pregnant	Hypersensitivity	Hypersensitivity	Hypersensitivity
Pediatric patients	Safety and efficacy have not been established in patients under age 15	Not studied	Not studied	Not studied
Elderly patients	Dosage individually titrated in PD, thus no specific adjustment for elderly			
Pregnancy & Lactation	Pregnancy Category B	Pregnancy Category B	Pregnancy Category C	Pregnancy Category C
Renal insufficiency	N/A	N/A	Requires dosage adjustment	N/A
Hepatic insufficiency	N/A	N/A	N/A	Monitor and dose with caution

Drug Interactions

Drug/food interactions - Both the non-ergot DAs have a slight potential to interact with food. Food does not affect the extent of ropinirole absorption, although its Tmax is increased by 2.5 hours when the drug is taken with a meal. Likewise, food does not affect the extent of pramipexole absorption while it does increase Tmax by approximately 1 hour. The clinical significance of this interaction is thought to be minimal, and both drugs are recommended to be given with food to avoid nausea in patients experiencing that side effect.

Drug/drug interactions - All of the DAs have the potential to interact with antipsychotic drugs (dopamine antagonist effect) and with other drugs that cause CNS depression.

A list of potential drug interactions, adapted from Drug Facts & Comparisons®, is included in table 9:

Table 9: Dopamine agonist drug interactions

Precipitant drug	Object drug *		Description
Ciprofloxacin	Ropinirole	↑	Co-administration of ciprofloxacin (500 mg BID) with ropinirole increases the AUC of ropinirole by 84% on average, and the Cmax by 60%.
Smoking	Ropinirole	↓	The effect of cigarette smoking on the oral clearance of ropinirole has not been studied. Smoking is expected to increase the clearance of ropinirole since CYP1A2 is known to be induced by smoking.
Theophylline	Ropinirole	↔	Although a CYP1A2 substrate, the co-administration of theophylline had no effect on ropinirole plasma levels. Ropinirole has not been shown to alter the pharmacokinetics of theophylline.
Other CYP1A2 drugs (e.g. cimetidine, ciprofloxacin, diltiazem, enoxacin, erythromycin, fluvoxamine, mexiletine, norfloxacin, tacrine)	Ropinirole	↑	May cause increases in serum concentrations of ropinirole.
Drugs eliminated via renal secretion (e.g. Cimetidine, ranitidine, diltiazem, quinidine, quinine, triamterine)	Pramipexole	↑	Coadministration of drugs that are secreted by the cationic transport system may decrease the oral clearance of pramipexole by > 20%.
Cimetideine	Pramipexole	↑	Cimetidine caused a 50% increase in pramipexole AUC and a 40% increase in its half-life.
Estrogen	Ropinirole	↑	Estrogens (mainly ethinyl estradiol, 0.6 to 3 mg over a 4-month to 23-year period) reduced the oral clearance of ropinirole by 36% in 16 patients.
Ropinirole, pramipexole	Levodopa	↑	Concomitant administration increased levodopa Cmax (20% to 40%); pramipexole Cmax decreased from 2.5 to 0.5 hours.

↑ = object drug increased; ↓ = object drug decreased; ↔ = undetermined clinical effect

Tolerability and Compliance Issues

The DA are generally well tolerated by patients requiring these medications for the treatment of Parkinson's disease. Nausea was the principal reason for discontinuation in controlled clinical trials of DA, while the principal side effect resulting in discontinuation in non-study patients is dyskinesia. The slow titration of the agents is beneficial in alleviating many of the adverse effects seen in clinical trials. .

All of the DA require carefully individualized dosage titration and all except pergolide require multiple daily dosing. Therefore, there are no anticipated differences with respect to compliance.

Conclusion

For a class of medications that have been in use for decades, there is a lack of well done/clearly reported studies. It is not possible to establish that any one drug is clearly superior or even equivalent to another. It is

clear, though, that the DA are considered to be first line therapy for Parkinson's in selected patients. There is evidence to support the use of a non-ergot dopamine agonist due to the development of valvulopathy with the ergot derived dopamine agonists.

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Appendix A: Detailed Literature Search Strategy

One of the literature searches used the Evidence Based Medicine Controlled Trials section in OVID with no date restriction to present. Search Strategy as follows:

Search for: limit 8 to english language [Limit not valid; records were retained]
Citations: 1-155

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2003>
Search Strategy:
---
1 Dopamine Agonists/ (163)
2 Bromocriptine/ (378)
3 Pergolide/ (42)
4 pramipexole.tw. (35)
5 ropinirole.tw. (35)
6 or/1-5 (574)
7 exp parkinsons disease/ (921)
8 6 and 7 (155)
9 limit 8 to english language [Limit not valid; records were retained] (155)
10 from 9 keep 1-155 (155)

Additionally, MEDLINE was searched from 1996 forward:

Search for: limit 8 to english language
Citations: 1-160

Database: MEDLINE <1996 to April Week 4 2003>
Search Strategy:
---
1 Dopamine Agonists/ (3180)
2 Bromocriptine/ (795)
3 Pergolide/ (156)
4 pramipexole.tw. (190)
5 ropinirole.tw. (151)
6 or/1-5 (3749)
7 exp parkinsons disease/ (8466)
8 6 and 7 (573)
9 limit 8 to english language (491)
10 from 9 keep 1-160 (160)

Search for: limit 8 to english language
Citations: 161-321

Database: MEDLINE <1996 to April Week 4 2003>
Search Strategy:

---
1 Dopamine Agonists/ (3180)
2 Bromocriptine/ (795)
3 Pergolide/ (156)
4 pramipexole.tw. (190)
5 ropinirole.tw. (151)
6 or/1-5 (3749)
7 exp parkinsons disease/ (8466)
8 6 and 7 (573)
9 limit 8 to english language (491)
10 from 9 keep 161-321 (161)
Search for: limit 8 to english language
Citations: 322-491

Database: MEDLINE <1996 to April Week 4 2003>
Search Strategy:
---
1 Dopamine Agonists/ (3180)
2 Bromocriptine/ (795)
3 Pergolide/ (156)
4 pramipexole.tw. (190)
5 ropinirole.tw. (151)
6 or/1-5 (3749)
7 exp parkinsons disease/ (8466)
8 6 and 7 (573)
9 limit 8 to english language (491)
10 from 9 keep 322-491 (170)

Appendix B: Detailed Clinical Trial Tables Parkinson's Disease

Efficacy and Safety Systematic Reviews of Individual DAs

Studies involving bromocriptine alone were done prior to the development of CONSORT (Consolidated Standards of Reporting Trials). The bromocriptine trials, unfortunately, demonstrate nearly every bias and fatal flaw which compromise a trial's results so much as to invalidate the study. This is evident in the Cochrane systematic review conclusions bulleted below. The studies involving pergolide, pramipexole and ropinirole, were also noted by Cochrane to have poor adherence to the CONSORT standards for reporting.

Results of Cochrane Systematic Reviews Involving Bromocriptine

- **BRO/LEV Combined VS LEV Alone for Early Parkinson's Disease**
  - Ramaker, C; Hilten, JJ van Cochrane Movement Disorders Group. Date of Most recent update: 26 Feb 2002
  - Severe methodological differences between studies render a quantitative meta-analysis impossible
    - No study provided intention to treat analysis
  - Large numbers of patients excluded from analysis after randomization invalidates the results.
  - There is no convincing evidence to support or refute the use of BRO/LEV combo therapy early in disease.
- **Bromocriptine for Levodopa-induced Motor Complications in Parkinson's Disease**
  - Hilten, JJ; van Ramaker, C; Beek, WJT, van de finken, MJJ Cochrane Movement Disorders Group. Date of Most recent update: 21 Nov 1998
  - Major methodological problems preclude a conclusion on the efficacy of BRO as an adjunctive TX in PD patients with motor complications.
    - No study provided intention to treat analysis

Comment [r3]: Cochrane Database of Systematic Reviews. Vol (1) 2003. Bromocriptine/levodopa combined versus levodopa alone for early Parkinson's disease. Vol (1) 2003.

Comment [r4]: Cochrane Database of Systematic Reviews. Vol (1) 2003. Bromocriptine for levodopa-induced motor complications in Parkinson's disease.

Table 10: Results of Studies Involving Pergolide

Reference (trial design)	Number of Patients	Trial Duration (wk)	Dosage (mg)	Primary Outcome	Results	Conclusions
PER for Levodopa-induced Complications in Parkinson's Disease						
Clarke, CE; Speller, JM Cochrane Movement Disorders Group. Date of Most recent update: 24 July 2001 Large multicenter dbl blind, parallel group RCT comparing PER with PBO This study was done in the 80's but not published in full until 1994	1 study with 376 patients	24 weeks	Mean dose 2.94 mg/d	1) improvement in time patients spend in the "off" state 2) Changes in the prevalence of dyskinesia and dyskinesia rating scales 3) Changes in parkinsonian rating scales 4) Reduction in LEV dose.	1) Mean time spent "off" was reduced by 1.8 hours with PER compared to 0.2 hours with PBO. (p<0.001) 2) Dyskinesia developed or deteriorated in 62% of PER pts compared with 25% PBO pts. 3) PER vs PBO showed sig diff in H&Y stages in both motor and ADL.	PER can be a useful adjunct to LEV to reduce "off" time, decrease Parkinson sxs and lower LEV dose, but this comes at the expense of an increase in dyskinesia and withdrawals

Comment [r5]: Cochrane Database of Systematic Reviews. Vol (1) 2003.

Analysis WAS intention-to-treat.				5) Number of withdrawals due to lack of efficacy and/or AEs	4) Mean LEV dose reduced 235 mg vs 51 mg for PER vs PBO (p<0.001) 5) Withdrawals due to AE 9.5% PER vs 4.3% PBO.	
Pergolide monotherapy in early Parkinson's Disease						
Barone, P et al Pergolide Monotherapy Study Group Dbl blind, parallel group, randomized, multicenter clinical trial Intention-to-treat analysis WAS done.	1 study with 112 patients in study, 105 randomized. 52 PBO 53 PER	3 months	Mean dose PER 2.06mg/d	1) response criterion = 30% reduction in UPDRS part III score between baseline and patient's last visit 2) AEs reported	1) 30 of 53 (56.6%) PER gp 9 fo 52 (17.3%) PBO gp p<0.001 2) 34/53 in PER 31/52 in PBO p=0.632	1) 95% CI 22.5- 56.1% 2) NS

Comment [r6]: Barone, P et al. Pergolide monotherapy in the treatment of early PD. A randomized, controlled study. Neurology 1999;53:573-579

PER = pergolide, PBO = placebo, LEV = levodopa, AE = adverse event, ADL = activities of daily living, H&Y = Hoehn and Yahr staging test, UPDRS = Uniform Parkinson's Disease Rating Scale

Table 11: Results of Studies Involving Pramipexole

Reference (trial design)	Number of Patients	Trial Duration (wk)	Dosage (mg)	Primary Outcome	Results	Conclusions
Pramipexole for levodopa-induced complications in Parkinson's disease						
Clarke, CE; Speller, JM Cochrane Movement Disorders Group. Date of Most recent update: 24 July 2001 2 phase III studies 2 phase II studies All RCT dbl blind, parallel group multicenter trials	4 studies for total of 669 patients with "later" PD	2 phase III studies (24 weeks maintenance) 2 phase II studies (4 weeks maintenance)	Mean average dose only given for 3 of the trials. (3.36mg/d, 3.59 mg/d and 4.59mg/d) 4.5-5mg/d maximum doses allowed in all trials for PPX 1 study did not allow LEV dose reduction	1) reduction in "off" time 2) change in dyskinesia rating scale and prevalence of dyskinesia 3) changes in parkinsonian rating scales 4) Reduction in LEV dose 5) number of withdrawals due to lack of efficacy and/or AEs	1) weighted mean difference 1.8 hour reduction with PPX vs PBO 2) NS in scale ratings, but dyskinesia reported as AE more frequently with PPX 3) sig improvement noted in 2 studies with no improvement noted in the other 2 studies regarding complication score Sig improvement in ADL scores for PPX in all studies 4) LEV dose reduction allowed in 3 studies with sig diff in favor of PPX 115mg PBO 5) ↓ PPX withdrawals	1) 1.2, 2.3 95% CI 2) numerous different scales used 3)Interpretations were considered difficult 4) 87, 143 95% CI PPX can reduce "off" time, improve motor impairment, reduce LEV dose but at the expense of increased dyskinesias for up to 24 weeks

PPX = Pramipexole, PBO = placebo, LEV = levodopa, AE = adverse event, ADL = activities of daily living

Comment [r7]: Cochrane Database of Systematic Reviews. Vol (1) 2003. Pramipexole for levodopa-induced complications in Parkinson's disease.

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Table 12: Results of Studies Involving Ropinirole

Reference (trial design)	Number of Patients	Trial Duration (wk)	Dosage (mg)	Primary Outcome	Results	Conclusions
Ropinirole for levodopa-induced complications in Parkinson's disease						
Clarke, CE; Deane, KHO Cochrane Movement Disorders Group. Date of Most recent update: 13 Nov 2000 3 dbl blind, parallel group RCTs	263 total patients	2 phase II studies (12 weeks) 1 phase III study (26 weeks)	Mean average dose of the 2 phase II trials only used sub-optimal doses of ROP (up to 8 or 10 mg/d) and could not be used in the meta-analysis Up to 24mg/d in a TID regimen was used in the phase III study	1) Reduction in "off" time 2) Change in dyskinesia rating scale and prevalence of dyskinesia 3) Changes in Parkinsonian rating scales 4) Reduction in LEV dose 5) Number of withdrawals due to lack of efficacy and/or AEs	1) Did not reach statistical significance when compared to placebo 2) Dyskinesia was not measured with rating scales in any of these trials. 3) Cochrane had to go to the manufacturer to get data on motor impairment as the reporting in the studies was poor. Manufacturer reported more pts "much" or "very much" improved on ROP compared to PBO. (OR 2.98; 1.53, 5.80; p=0.001) 4) LEV dose reduction was shown in 2 studies and could be reduced significantly more with ROP than with PBO. (WMD 180 mg/d; 106, 253 95% CI) 5) There was a trend toward fewer dropouts in the ropinirole group compared to PBO but it did not achieve statistical significance. There were more dyskinesias reported as an AE in the ROP group. (OR 2.90; 1.36, 6.19 95% CI)	1) NS 2) No scales used 3) Poor reporting 4) LEV can be reduced with use of ROP 5) Ropinirole can reduce LEV dose but at the expense of increased dyskinesias for up to 26 weeks
Ropinirole for the treatment of early Parkinson's disease						
Adler, CH et al Prospective dbl-blind, parallel group RCT with limited or no prior dopaminergic TX (could be on selegeline)	241 patients	6 months	Up to 24 mg/d in 3 divided doses. If on selegeline, had to remain on the same dose throughout the study. If on maximal therapy of ROP or PBO and still symptomatic, open-label LEV was added to the blinded study med. At study end, 11% of ROP and 29% of PBO patients were on LEV	1) % improvement in UPDRS motor score	1) Improvement in motor function as measured by UPDRS for ROP vs PBO 17.9 ± 8.8 (base) to 13.4 ± 9.5 (end) VS 1.17 ± 9.5 (base) TO 17.9 ± 10.5 at end (end) 2) ROP-treated patients had a greater percentage improvement than PBO patients. 3) Dropouts due to AEs: 27/116 ROP and 13/125 PBO nausea most common AE leading to dropout (52.6% c/o nausea, but only 6.9% withdrew due to it for ROP)	1) 24% improvement of score for ROP vs 3% worsening of score for PBO 2) +24% vs –3% (p<0.001)

ROP = ropinirole, PBO = placebo, LEV = levodopa, AE = adverse event, ADL = activities of daily living, UPDRS = Uniform Parkinson's Disease Rating Scale

Comment [r8]: Cochrane Database of Systematic Reviews. Vol (1) 2003. Ropinirole for levodopa-induced complications in Parkinson's disease

Comment [r9]: Adler, C.H. MD, PhD et al. Ropinirole for the treatment of early Parkinson's disease. Neurology. Vol 49(2) Aug 1997. pp 393-399.

Meta-analyses & Systematic Reviews

Table 13: Results of Cochrane Systematic Reviews comparing efficacy and safety of bromocriptine with the other DAs for levodopa-induced complications in patients with Parkinson's (adjunctive therapy)

Reference	Number of Trials & Patients	Trial Duration (wk)	Dosage Range (mg)	Primary Outcomes	Results	Conclusions
Efficacy and Safety of Pergolide (PER) vs bromocriptine (BRO) (adjunctive to levodopa)						
Clarke, CE;Speller, JM. Cochrane Movement Disorders Group. Date of Most recent update: 24 July 2001	3 short-term RCTs Japanese 191 patients dbl blind Italian 114 patients open label Danish 33 patients blind rater	Japanese (8 weeks) Italian and Danish (12-week crossover trials)	Up to 2.25mg of PER in one study Up to 5mg PER in 2 studies Up to 22.5mg* BRO in one study Up to 50mg BRO in 2 studies	1)Improvement in time pts spend in "off" state 2) Changes in dyskinesia rating scales and prevalence of dyskinesia 3) Changes in parkinsonian rating scales 4) Reduction in levodopa dose 5) Number of withdrawals due to lack of efficacy and/or AEs	1) and 2) Insufficient evidence on "on-off" fluctuations or dyskinesias to draw any conclusions 3) PER superior to BRO in 2 trials 4) No significant difference 5) No differences in all cause dropout rates	As different rating scales used for each study, cannot combine efficacy results in a quantitative manner
Efficacy and Safety of Pramipexole(PRP) vs bromocriptine (adjunctive to levodopa)						
Clarke, CE; Speller, JM Clarke, JA Cochrane Movement Disorders Group Date of Most recent update: 24 July 2001	1 RCT dbl blind, parallel group with PBO arm	12 weeks titration then 24 weeks maintenance 79 PRP pts with 16 dropouts due to AE 84 BRO pts with 17 dropouts due to AE 83 PBO pts with 33 dropouts	Up to 4.5mg/d PRP Up to 30mg/d** BRO	Same as above	1) Improvement in "off" state with PRP by average of 1.4 hours over BRO 2), 3), 4), 5) No significant difference could be demonstrated due to lack of power	Study not powered to examine differences between active TX arms

Comment [r10]: Cochrane Database of Systematic Reviews. Vol (1) 2003. Pergolide versus bromocriptine for levodopa-induced complications in Parkinson's disease.

Comment [r11]: Cochrane Database of Systematic Reviews. Vol (1) 2003. Pramipexole versus bromocriptine for levodopa-induced complications in Parkinson's disease.

		mainly due to worsening of PD sxs				
Efficacy and Safety of ropinirole (ROP) vs bromocriptine (adjunctive to levodopa)						
Clarke, CE; Deane, KH Cochrane Movement Disorders Group Date of Most recent update: 27 Feb 2002	3 RCTs Murayama and Brunt both were dbl blind, parallel group Im was randomized, Open-label Parallel group	Murayama 8 weeks 132 ROP pts with 27 dropouts 135 BRO pts with 35 dropouts Im 16 weeks 37 ROP pts with 5 dropouts 39 BRO patients with 6 dropouts Brunt 25 weeks 367 ROP pts with 68 dropouts 188 BRO pts with 36 dropouts No details for termination given	Im and Murayama Up to 9mg ROP# Brunt Up to 24mg/d ROP Im Up to 17.5mg/d BRO Murayama Up to 22.5mg/d BRO Brunt Up to 39.9mg/d BRO	Same as above	Studies not powered to detect clinically relevant differences	1) No statistical difference in "off" time between ROP and BRO 2) Dyskinesia rating scale not used 3) No difference between the 2 agents 4) No sig diff between DAs 5) Withdrawal rates comparable except less nausea with ROP – but usage of domperidone was not documented

Comment [r12]: Cochrane Database of Systematic Reviews. Vol (1) 2003. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease.

∗A low dose of bromocriptine by American and European standards, but usual practice amongst Japanese neurologists
∗∗A low dose of bromocriptine by American and European standards
ROP = ropinirole, PBO = placebo, LEV = levodopa, AE = adverse event, ADL = activities of daily living, BRO = bromocriptine

Appendix C: Detailed Clinical Trial Tables: Restless Leg Syndrome

Reference	Agent	Study Design	Trial Design	Dosage (mg)	Results	Safety	Conclusions
Walters, et al. 1988	BRM	Double blind randomized crossover	6 pts	BRM 7.5 mg	Decrease in PMS per night and per hour of sleep as measured by polysomnograph (p<0.025 versus placebo)	Only seen in 1 patient- nasal stuffiness and lightheaded	Effective therapy
Staedt, et al. 1997	PER versus levodopa	DB, R crossover	11 pts	PER 0.125 mg Levodopa 250 mg	Increased total sleep time (p<0.001)	Minor, no withdrawals	Pergolide was superior to levodopa/carbidopa in retreatment of RLS
Pieta, et al. 1998	PER	DB, PC,Crossover	8 pts on chronic HD	PER mean dose 0.25mg	Subjective improvement on 62.5% of patients (5/8)	3 withdrawals due to nausea, vomiting or nightmares	Objective results not confirmed as measured by polysomnograph
Wetter, et al. 1999	Pergolide	R, DB, PC crossover	28 pts	PER mean dose 0.51 mg all patients received dromperidone 20 mg TID	PLMS decreased p<0.0001 (438 vs 45.7 with PER) Sleep efficiency improved p=0.0001) Severity Scales and QOL instruments also favored PER	Most frequent were nausea, headache and rhinitis. No withdrawals were due to AE	Highly effective in treating sensorimotor symptoms and sleep disturbances of RLS
Silber, et al. 1997	PER	Open label	20 patients, prior therapy for RLS	PER mean 0.26 mg	Complete control of symptoms in 45% , moderate control in 50%	12/20 experienced AE, 5 withdrawals due to AE. Dizziness, insomnia and constipation most common	Effective for levodopa induced daytime augmentation for RLS. Tolerance did not develop. Appropriate second line therapy for RLS

Earley, et al. 1998	Pergolide	R, DB, PC, parallel	16 pts , 9 on current therapy for RLS	PER mean dose 0.35 mg	PLMS decreased from 48.9 to 14.5 (p<0.05) Global improvement score 61% vs 19% (p=0.009)	Stomach pain, increased dreams, constipation no treatment withdrawals due to AE	PER treated patients showed significant improvement in clinical and objective measures
Stasny, et al. 2001	PER	Open label followup to Winkelmann trial	28 pts	PER mean dose 0.37mg	PLMS index, arousal index, total sleep time and sleep efficiency all improved with treatment (p=0.0001)	Nausea most common, well controlled with domperidon e	Augmentation developed in 27% of patients Did not result in increased dose of PER.
Winkelmann, et al. 1998	PER	Open label	15 patients	PER mean dose 0.4mg	Subjective measures all showed improvement. Patients demonstrated less restlessness, better sleep	Most frequent stuffy nose, nausea	Reported efficacy in idiopathic and uremic patients
Stiansy et al, 2000	PMX	Case series	24 adult outpatients surveyed by mail survey with phone followup	PMX mean dose 0.37mg Range 0.125-0.75	50% rated very much better, 38% much better 33% very satisfied, 38% markedly satisfied	Chronic daytime fatigue reported in 11 of 24, sleep episodes reported in 5/24	Results promising, Should be evaluated with larger controlled trials
Montplaisir, et al. 2000	PMX	Followup to trial from 1999	7 pts		No decrease in benefit after mean 7.8 months of therapy Decrease in RL at bedtime and nightime	Nausea and daytime sleepiness reported in one patient	Low dose PMX effective in RLS
Montplaisir, et al. 1999	PMX	R, DB, PC, Crossover	10 pts	PMX initiate at 0.375 mg titrate uo over 4 weeks to 1.5 mg administere d 1 hr before bedtime	PLMS baseline 465, placebo 452, PMX 10.6 arousal index baseline 137 placebo103 PMX 0.8	GI effects reported in 9/10, daytime fatigue 3/10	PMX reduced PLMS index to normal (p=0.005). Alleviated leg discomfort measured by questionnaires

Becker, et al. 1998	PMX	Open trial	23 pt who had received prior therapy for RLS	PMX two titration schemes O.125 mg initial then double dose every week or every 3 days till improvement	PMX preferred med in 17 of 23 pts as assessed by International RLS Study Group questionnaire (p<0.0001)	4 treatment withdrawls	Needs larger controlled trial to confirm
Lin, et al. 1998	PMX	Consecutive series	16 with RLS refractory to levodopa or pergolode	PMX mean dose 0.3mg	Improvement in Visual analog scale at 2-3 months of therapy for nocturnal RLS, insomnia	Fatigue, stiffness in 33%	Effective treatment
Saletu, et al. 2002	PMX	Single blind placebo control	11 pts part one acute blinded, part two open followup	PMX mean 0.28mg	Total number of PLMS reduced by 63%(p=0.005) Sleep architecture improved (p=0.002)	Minor reports of nausea, headache and vertigo	PMX markedly reduced PLM measures and significantly improved objective and subjective sleep quality, QOL
Galvez-Jimenez, 1999	PMX or ROP	Case series	6 adults with drug resistant RLS(4 used PMX, 2 used ROP)	PMX mean 0.75 mg/d ROP mean 3.5mg/d	On a scale of 0(normal) to 24(severe) RLS rating was 10.3 after 9 months of treatment	Dry mouth	PMX useful in controlling RLS
Trenkwalder, et al. 2004	ROP	R, Placebo control	284 patients	ROP 0.25-4.0 mg	Improvement in International Restless Legs Scale better with ROP (p=0.0036) Clinical Global Impression Scale better with ROP (p=0.0416)	Nausea, headache	ROP improved symptoms of RLS in comparison to placebo, these results were evident by week 1
Ondo, 1999	Ropinirole	Open label	16 pts, both primary and secondary	Ropinirole 2.8 mg mean dose	IRLSSG questionnaire showed improvement 18.6 to 7.7 p< 0.00000001)	3 withdrawals due to AE most common AE were sedation, nausea, dyspepsia	Encouraging results , need to be demonstrated with a larger controlled study.

Galvez-Jimenenz, 1999	Ropinirole	Case series	8 pts	Ropinirole 2.8 mg mean dose	IRLSSG questionnaire showed improvement	None reported	Supported results seen by Ondo, 1999. Need a trial comparing PMX and ropinirole