

by Margaret Asquith, PharmD, Pharmacy Practice Resident
and Kari Egan, Doctor of Pharmacy Candidate

Column Editor: Lee Vermeulen, MS, RPh,
Director, Center for Drug Policy, University of Wisconsin Hospital and Clinics

Pramipexole and Ropinirole

New dopamine agonists for Parkinson's Disease

Introduction

Idiopathic Parkinson's disease is a neurodegenerative condition characterized by tremor, bradykinesia, rigidity, and postural instability. This chronic disease is caused by a loss of the neurotransmitter dopamine in the nigrostriatal pathway. These neurons are part of a complex system of neurons that regulate voluntary motor movement. The symptoms of Parkinson's disease typically become apparent when 60% to 70% of the dopamine producing neurons are lost.¹ As the patient ages, more neurons are lost leading to progressively worsening disease. The reason for the selective loss of these neurons is poorly understood. Over one million people have Parkinson's disease in North America and increasing age is the primary risk factor. Parkinson's disease affects approximately 1% of the US population over 50 years old.² Currently, there is no cure for Parkinson's disease. Although surgical interventions can be helpful, therapy is primarily pharmacologic, focusing on symptom relief through the replacement of dopamine in the substantia nigra.

The most commonly used agent is levodopa, a prodrug which is converted in both the central nervous system and the periphery to dopamine. The formation of dopamine within the central nervous system corrects the underlying neurotransmitter imbalance and eases Parkinson's symptoms. Peripheral conversion of levodopa to dopamine results in severe nausea, hypotension, and dizziness. The decarboxylase inhibitor carbidopa is added to formulations of levodopa to block this peripheral conversion. Its short half-life, side effects and long-term complications limit the usefulness of levodopa. Because levodopa has a short half-life, it requires multiple doses per day which can be inconvenient for the patient and result in compliance problems. Major side effects of levodopa include hallucinations, gastrointestinal disturbances, hypotension, somnolence, and dyskinesias. Adverse effects associated with long-term use of levodopa include motor fluctuations (wearing-off and on-off fluctuations).^{1,3}

Anticholinergic drugs, including trihexyphenidyl (Artane® – Lederle), benzotropine (Cogentin® – MSD), biperiden (Akineton® – Knoll), and ethopropazine (Parsidol® – Parke Davis), are used to treat Parkinson's disease, especially if tremor is the predominant symptom. The decrease in striatal dopamine which occurs in Parkinson's patients leads to a

pseudo-increase in striatal acetylcholine. Anticholinergic agents correct this imbalance. Unfortunately, anticholinergic agents can have significant side effects such as dry mouth, blurred vision, constipation, urinary retention, confusion decrease in memory, and hallucinations.^{1,3}

The monoamine oxidase B inhibitor selegiline (Eldepryl® - Somerset) is also useful in the adjuvant treatment of Parkinson's disease. Selegiline inhibits the breakdown of dopamine in the brain. As monotherapy, selegiline is not an effective treatment for Parkinson's disease; however, when used in combination with levodopa, selegiline increases the duration of action of levodopa and can lead to a reduction in levodopa doses.³

Amantadine (Symmetrel® - Endo Labs) is an antiviral agent with some antiparkinson effects. The exact mechanism in Parkinson's disease is unknown. Amantadine is well tolerated but has limited efficacy. It is used for monotherapy in early disease and as an adjuvant to levodopa. The therapeutic benefits are short and usually decrease after a few months of therapy.³

Tolcapone (Tasmar® – Roche) is a unique drug recently approved for the treatment of Parkinson's disease. It is an orally active inhibitor of the catechol-*O*-methyltransferase (COMT) enzyme and is used as an adjunct to levodopa/carbidopa therapy. COMT is one of the enzymes responsible for the central and peripheral metabolism of catecholamines. The concurrent administration of a COMT inhibitor such as tolcapone with levodopa/carbidopa enhances levodopa bioavailability, increases the amount of levodopa brain penetration, and increases the elimination half-life of levodopa. This results in prolonging the clinical effect of levodopa and improving motor function in patients with or without the "wearing-off" phenomena. The clinical benefit of tolcapone is sharply limited by its risk of hepatotoxicity (see sidebar on page 24 for additional information).

Dopamine agonists (not structurally related to levodopa) are the ergot alkaloids bromocriptine (Parlodel® – Novartis)

Margaret Asquith, PharmD, is a pharmacy practice resident in the Department of Pharmacy, University of Wisconsin Hospital and Clinics. Kari Egan is a doctor of pharmacy candidate at the University of Wisconsin-Madison School of Pharmacy.

and pergolide (Permax® – Athena). These are the first generation dopamine agonists and are used as an adjuvant to levodopa for advanced Parkinson's disease and, more recently, as monotherapy for early disease.^{4,5} These agents are used to reduce the motor fluctuations ("on-off" and "wearing-off" effects) of levodopa and to reduce the levodopa requirements. Their usefulness is limited by various side effects including nausea, dizziness, somnolence, orthostatic hypotension, hallucinations, and dyskinesias. Their use is also associated with more serious side effects such as lower limb edema, pleuropulmonary fibrosis, and retroperitoneal fibrosis. Potential advantages of dopamine agonists over levodopa are an increase in dopamine-2 (D2) receptor selectivity, longer duration of action, possible neuroprotection due to a lack of oxidized metabolites, increased therapeutic window, decreased risk of dyskinesias, and decrease in dose level fluctuations.

Recently, two non-ergoline dopamine agonists, pramipexole (Mirapex® - Pharmacia & Upjohn) and ropinirole (Requip® – SmithKline Beecham), have been approved for use in the United States. These second-generation dopamine agonists lack the ergot structure of the older agents. The purpose of this paper is to review the pharmacology, pharmacokinetics, efficacy, tolerability, and cost of these new drugs.

Pharmacology/Pharmacokinetics

Pramipexole and ropinirole are non-ergot dopamine agonists which are selective for the D2 subfamily of dopamine receptors. Loss of dopamine producing neurons in the substantia nigra leads to the motor features of Parkinson's disease.⁶

Pramipexole

Pramipexole has an absolute bioavailability of approximately 90% indicating little presystemic metabolism.⁷ The drug is rapidly absorbed after oral administration and reaches peak concentrations in approximately 2 hours. Food does not affect the extent of absorption but can delay the time to peak concentrations by approximately 1 hour. Pramipexole is 15% bound to plasma proteins and has a volume of distribution of 500 L. The drug displays linear kinetics over the clinical dosing range. Its terminal half-life in healthy adults is 8 hours, in patients over 65 years of age the half-life increases to 12 hours. Pramipexole is secreted by the renal tubules and its renal clearance is approximately 400 ml/min. Urinary excretion is the primary route of pramipexole elimination with 90% of the unchanged drug recovered in the urine.

Ropinirole

Absorption of ropinirole is rapid following oral administration.^{8,9} Peak concentration is reached in 1 to 2 hours. Food does not affect the extent of absorption. However, time to maximum absorption is delayed by 2.5 hours when given with food. First pass metabolism has been noted. Clearance following oral administration is 47 L/hr and the elimination half-life is

approximately 6 hours. Metabolism by the liver to inactive metabolites is extensive, and linear kinetics are effective over the therapeutic dosing range of 1 mg to 8 mg three times daily. Cytochrome P450 1A2 is the major isoenzyme involved in the hydroxylation and dealkylation of ropinirole. Ropinirole is widely distributed throughout the body with an apparent volume of distribution of 7.5 L/kg. Ropinirole is 40% bound to plasma proteins.

Clinical Trials

Pramipexole

Hubble et al evaluated the efficacy, safety, and tolerability of pramipexole in 55 patients with early Parkinson's disease (Hoehn and Yahr stage I to III) who were not receiving levodopa.¹⁰ This was a multicenter, prospective, double-blind, randomized, placebo-controlled, parallel-group study. Primary endpoints were the mean change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) part II [(activities of daily living (ADL)] and part III (motor exam). Patients were taking selegiline 5 mg twice daily and could take anticholinergic medications; other antiparkinsonian medications were not allowed. The study medication was slowly increased over 6 weeks to a maximum maintenance dose of 1.5 mg three times daily (4.5 mg daily). If dose-limiting adverse effects developed, the maximum tolerated dose was used as the maintenance dose. The maintenance phase lasted 3 weeks followed by a one week dose reduction phase. Pramipexole-treated patients demonstrated significant improvements from baseline in the final UPDRS ADL score at the end of the maintenance period (-5.19, $p=0.002$) and the average UPDRS ADL score from all maintenance visits (-4.84, $p=0.005$). Changes in UPDRS motor ratings at the final visit (-11.97, $p=0.1$) and the average of all maintenance visits (-11.96, $p=0.08$) did not reach statistical significance. All patients in both the placebo and the pramipexole groups experienced at least one episode of asymptomatic orthostatic hypotension. Other side effects included symptomatic orthostatic hypotension, dizziness, headache, nausea, insomnia, and hallucinations.

The safety and efficacy of pramipexole in patients with mild to moderate Parkinson's disease who were not receiving levodopa was evaluated in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study.¹¹ The primary end points were changes in UPDRS ADL and motor scores. Selegiline was allowed if the dose had been stable for 30 days prior to study entry. Pramipexole was gradually titrated to a target dose of 4.5 mg per day or to the maximum tolerated dose. The mean maintenance dose was 3.8 mg per day. There were 335 subjects randomized and 333 included in the statistical analysis (163 pramipexole and 170 placebo). Patients receiving pramipexole demonstrated significant improvements in UPDRS ADL (8.2 at baseline vs 6.4 at end of maintenance;

$p=0.002$) and motor subscales (18.3 at baseline vs 14.1 at end of maintenance) ($p < 0.0001$). Significant improvements were noted at week 3 of the dose-escalation phase and were maintained throughout the course of the study. No changes from baseline were noted in the placebo patients. Nausea (39% vs 20.5%; $p=0.0002$), insomnia (25.6% vs 12.9%; $p=0.0034$), constipation (17.7% vs 6.4%; $p=0.0021$), somnolence (18.3% vs 8.8%; $p=0.015$), and visual hallucinations (9.7% vs 2.3%; $p=0.0048$) occurred significantly more often with pramipexole compared to placebo.

Lieberman and colleagues evaluated pramipexole in 360 patients with advanced Parkinson's disease (Hoehn and Yahr stage II-IV) who were experiencing motor fluctuations while receiving a stable dose of levodopa.¹² This was a multicenter, double-blind, placebo-controlled, parallel-group study. The primary endpoints were the change from baseline in UPDRS ADL and motor scores. Anticholinergic medications, selegiline, and amantadine were allowed and patients were required to be stabilized on levodopa for at least 30 days prior to the study. During the study the levodopa dose could be decreased but not increased beyond the baseline dose. Pramipexole was titrated over a six-week period to a maximum of 4.5 mg per day. Pramipexole demonstrated a significant improvement compared to placebo with respect to UPDRS ADL ratings (-22% for pramipexole vs -4% for placebo; $p \leq 0.0001$) and UPDRS motor ratings (-25% for pramipexole vs -12% for placebo; $p=0.01$). According to patient diaries, the average time spent "off" decreased by 31% in the pramipexole patients and 7% in the placebo patients ($p=0.0006$). The average severity of time spent off decreased by 17% in the pramipexole patients and 5% in the placebo patients ($p=0.01$). No improvements were demonstrated for the UPDRS part I and part IV, the Parkinson Dyskinesia Scale, or timed walking tests. The pramipexole patients had significantly greater reductions in the total levodopa dose than placebo patients when compared to baseline. There was a significantly greater decrease in the mean levodopa dose with pramipexole compared to placebo (229.68 mg vs 43.20 mg; $p \leq 0.0001$). Adverse events occurred in 94.5% and 88.3% of the pramipexole and placebo patients, respectively. The most frequently reported adverse events were dyskinesia (61.3%), asymptomatic orthostatic hypotension (48.1%), dizziness (36.5%), insomnia (22.7%), hallucinations (19.3%), nausea (17.7%), symptomatic orthostatic hypotension (16.0%), and confusion (11.0%). A total of 54 patients (15%) withdrew from the study due to adverse events (24 for pramipexole and 30 for placebo).

Wermuth et al investigated whether pramipexole has a levodopa-sparing effect, and whether pramipexole could decrease the motor fluctuations experienced by patients in late stage Parkinson's disease treated with levodopa.¹³ The study included patients with advanced Parkinson's disease who had

Tolcapone (Tasmar® - Roche)

Indications: Tolcapone (Tasmar® - Roche) is a selective and reversible inhibitor of catechol-O-methyltransferase indicated for use as an adjunct to levodopa in the treatment of idiopathic Parkinson's disease. Because of the risk of potentially fatal, acute, fulminant liver failure, tolcapone should only be used in patients with Parkinson's disease on levodopa/carbidopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not candidates for other adjunctive therapies. Tolcapone should not be initiated in patients exhibiting clinical evidence of liver disease or two serum glutamic-pyruvic transaminase (SGPT/ALT) or serum glutamic-oxaloacetic transaminase (SGOT/AST) values greater than the upper limit of normal.

Monitoring Parameters: Several cases of severe hepatocellular injury, including fulminant liver failure resulting in death, have been reported in post-marketing use. Monitor SGPT/ALT and SGOT/AST levels at baseline and then every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months, and then every 8 weeks thereafter. If the dose is increased to 200 mg three times a day, liver enzyme monitoring should be done before increasing the dose and then be re-initiated at the frequency above. Tolcapone should be discontinued if the SGPT/ALT or SGOT/AST exceed the upper limit of normal or if clinical signs and symptoms suggest the onset of hepatic failure (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, and right upper quadrant tenderness). Patients who develop evidence of hepatocellular injury while on tolcapone and are withdrawn from the drug for any reason may be at increased risk for liver injury if tolcapone is reintroduced. Accordingly, such patients should not ordinarily be considered for re-treatment. Patients should be advised of the need for self-monitoring for both the classical signs of liver disease (e.g., clay-colored stools, jaundice) and the nonspecific ones (e.g., fatigue, loss of appetite, lethargy). Since the therapeutic effect of tolcapone is apparent within 3 weeks of starting treatment and because of the risk of liver failure, tolcapone should be withdrawn in patients who fail to demonstrate clinical benefit after 3 weeks of treatment. The most common side effects in clinical trials were dyskinesia, nausea, sleep disorder, anorexia, and hallucinations.

Dose: 100 to 200 mg by mouth three times daily with or without meals

Pediatrics: Safety and efficacy in pediatrics have not
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been studied.

Geriatrics: No changes in dose are recommended on the basis of advanced age.

Pregnancy Category: C. In animal studies, an increased rate of abortion, and impaired growth and learning development were observed in the offspring of rats and rabbits receiving daily doses of 100 mg/kg.

Breast Feeding: In animal studies, tolcapone was excreted in breast milk. It is unknown whether the drug is excreted in human milk.

Cost: Tolcapone is available as 100 mg and 200 mg tablets. The average wholesale price for a one-month supply of 100 mg tablets is \$162. The average wholesale price for a one-month supply of 200 mg tablets is \$174.

Discussion: Levodopa, a dopamine precursor, has become the gold standard of symptomatic treatment for patients with Parkinson's disease. Complications associated with long-term treatment with levodopa include the development of the "wearing-off" phenomenon, manifested as motor fluctuations and dyskinesias. The main strategies to counter the "wearing-off" phenomenon have been lower doses given more frequently, the use of controlled-release preparations of levodopa/carbidopa, and the coadministration of dopamine agonists. However, these approaches are not always successful.

Tolcapone was recently approved for the treatment of Parkinson's disease. It is an orally active inhibitor of the catechol-*O*-methyltransferase (COMT) enzyme and is used as an adjunct to levodopa/carbidopa therapy. When used as adjunctive treatment, tolcapone helps improve the therapeutic response to levodopa by prolonging the action of levodopa/carbidopa and improving motor function in patients with or without the "wearing-off" phenomenon.

Several cases of severe hepatocellular injury, including fulminant liver failure resulting in death, have been reported in post-marketing use. As of October 1998, 3 cases of fatal fulminant hepatic failure have been reported from approximately 60,000 patients providing about 40,000 patient years of worldwide use. This incidence may be 10- to 100-fold higher than the background incidence in the general population. Underreporting of cases may lead to significant underestimation of the increased risk associated with the use of tolcapone.

Because of the risk of hepatic damage, tolcapone should only be used in patients who are not responding satisfactorily to or are not candidates for other adjunctive therapies.

developed dyskinesias, "on-off" fluctuations, dystonia, akinesia, or end-of-dose deterioration while taking levodopa. This was a double-blind, placebo-controlled, randomized, multicenter trial in 69 patients. Levodopa doses could be decreased if symptoms of dopamine overstimulation developed (dyskinesias, confusion, hallucinations, and agitation). Study endpoints included the Schwab-England Disability Scale during "on" and "off" periods, intensity of dyskinesia during "on" periods using the Parkinson's Dyskinesia Scale, levodopa requirements during therapy and patient diaries of "off" times. Pramipexole patients had a significant decrease in UPDRS total score as compared to baseline, (-16.9±14.9; $p=0.0184$). The change in UPDRS total scores from baseline was not significant in the placebo group (-9.0±16.1). Using the Schwab-England scale for "on-off" periods, pramipexole patients had a 10% decrease in time spent "off" during waking hours. Placebo patients had a decrease of 3%. At the end of the maintenance period fewer pramipexole patients were reporting end of dose deteriorations than placebo patients. Levodopa requirement decreased in the pramipexole treated patients but not significantly. During the study 89% of pramipexole-treated patients and 76% of placebo treated patients experienced at least one adverse event. The most common side effects (>10%) were dizziness, insomnia, nausea, and postural hypotension.

Ropinirole

The efficacy and safety of ropinirole were evaluated in a multicenter, prospective, double-blind, parallel-group, 6-month study in 241 patients with early Parkinson's disease (Hoehn and Yahr stages I - III).¹⁴ Patients could not have used either levodopa or dopamine agonists within 6 weeks prior to the start of the study. Selegiline use was allowed, but dose adjustments and new starts were not permitted. Other antiparkinsonian drugs were discontinued at least 4 weeks prior to initiation of the study. After stratification for selegiline use, patients were randomized to receive either ropinirole 0.25 mg three times daily or an identical placebo. Weekly titration continued until symptoms were controlled. The minimum dose was 1.5 mg three times daily, and the maximum was 8 mg three times daily. Levodopa/carbidopa was started in patients who continued to experience symptoms after being titrated to the maximum dose of study drug.

Changes in the UPDRS motor examination scores constituted the primary outcome measure. Secondary outcomes included the percentage of patients with at least a 30% reduction in the UPDRS motor score (responders), the percentage of patients who were much (score=2) or very much (score=1) improved on the Clinical Global Impression (CGI) scale, and the percentage of patients who received rescue levodopa/carbidopa therapy. Adverse events were recorded and coded according to the WHO Adverse Reaction Terminology dictionary.

nary in order to evaluate safety and tolerability.

The UPDRS motor examination scores improved by 24% from 17.9 ± 8.8 at baseline to 13.4 ± 9.5 at endpoint in the ropinirole-treated patients. The UPDRS motor scores worsened by 3% in the placebo group (17.7 ± 9.5 at baseline to 17.9 ± 10.5 at endpoint). The difference from baseline to endpoint was significant. Results were similar between patients receiving selegiline and those not receiving selegiline. Significantly more ropinirole patients responded to treatment compared to placebo (20%) (Odds ratio = 4.45; 95% CI: 2.26, 8.78). When the results were stratified on the basis of selegiline therapy, there was a significantly greater percent of responders in the ropinirole group versus placebo (56% vs 14%; $p=0.008$). Ropinirole was also favored in the non-selegiline stratum, but this difference was not statistically significant. Analysis of the CGI ratings found 33% of ropinirole-treated patients were very much improved or much improved as compared to 12% in the placebo group (odds ratio = 4.06; 95% CI: 2.00, 8.22). Rescue levodopa was required in only 11% of ropinirole-treated patients compared to 29% of placebo patients (odds ratio = 0.30; 95% CI: 0.14, 0.61).

The most common adverse events reported by patients in the ropinirole and placebo groups, were nausea (52.6% vs 21.6%), dizziness (36.2% vs 18.4%), somnolence (36.2% vs 4.8%) and headache (17.2% vs 15.2%).

Patients who completed the initial 6-month study could opt to enter a 6-month extension study.¹⁵ Of the 184 patients completing the initial study, 147 participated in the 6-month extension (ropinirole, $n=70$; placebo, $n=77$). The primary endpoint was the percentage of patients completing the full 12-month study without requiring levodopa therapy. Other measures included the proportion of patients with an insufficient therapeutic response defined as the initiation of levodopa or withdrawal from either 6-month study due to lack of efficacy and the proportion of patients requiring symptomatic levodopa therapy.

Levodopa therapy was initiated in significantly fewer patients receiving ropinirole vs placebo (44% vs 22.4%; $p<0.001$). Significantly fewer ropinirole-treated patients demonstrated an inadequate therapeutic response as compared to placebo ($p<0.001$). Following the 12-month study, additional symptomatic levodopa therapy was required by only 19% of the ropinirole group versus 45.6% of the placebo group (odds ratio = 0.28; 95% CI: 0.1, 0.5; $p<0.001$). No interaction was noted between the selegiline strata and treatment group for any efficacy variable. The UPDRS scores were lower for ropinirole-treated patients as compared to placebo-treated patients at weeks 24 and 48. During the 12 months, greater proportions of ropinirole-treated patients were rated as very much improved or much improved on the CGI scale at weeks 24 (66%) and 48 (61.2%) as compared to those treated with placebo (32.1% and

17.9%, respectively). During the 6-month extension study, 93.2% of patients reported having experienced ongoing or emergent adverse effects including nausea, dizziness and somnolence.

Ropinirole was evaluated as an adjunct to levodopa/carbidopa in 149 patients with motor fluctuations.¹⁶ This was a 6-month, multicenter randomized, double-blind, placebo-controlled study. Patients had Hoehn and Yahr stage II - IV Parkinson's disease in the off state and had evidenced good response to levodopa complicated by predictable motor fluctuations with or without dyskinesia. Patients experiencing on-off phenomena as evidenced by an abrupt and unpredictable loss of efficacy unrelated to the timing of levodopa administration were excluded. Patients were stratified on the basis of concomitant selegiline.

Ropinirole doses were gradually titrated from 0.75 mg per day at baseline to a maximum dose of 24 mg per day. The minimum daily dose was 7.5 mg. After patients reached 7.5 mg per day, the levodopa/carbidopa dose was decreased by one-half to one tablet for each increase in study medication. If Parkinson's disease symptoms increased, the study medications could be increased. If after two increases in the study medication, the symptoms did not decrease, the dose of levodopa/carbidopa could be increased. If adverse effects appeared relating to excess dopaminergic stimulation, the levodopa/carbidopa was decreased and labeled as an unplanned dose reduction. If symptoms persisted, the study medication could be decreased.

Evaluation was carried out at baseline and at every study visit. Planned and unplanned changes in levodopa doses were recorded along with CGI evaluation and home diary entries 2 days before each visit. The primary endpoint for efficacy was the number of patients who achieved a 20% or greater decrease in levodopa dose and a 20% or greater reduction in the percent of time spent "off" between the baseline and final visits. Planned and unplanned reductions in levodopa and the change in total daily levodopa dose were analyzed separately as secondary endpoints along with changes from baseline to final visit in the percent of the waking day in the "off" state and the CGI scores. Statistical analysis was done on an intent-to-treat basis.

The percentage of patients who achieved a 20% or greater decrease in levodopa dose and a 20% or greater reduction in the percent of time spent "off" between the baseline and final visits was 35% of ropinirole patients compared to 13% of placebo patients ($p=0.002$). When the patients with unplanned levodopa dose reductions due to adverse effects were excluded from analysis, the primary endpoint was still achieved in 27.7% of the ropinirole group and 11.1% of the placebo group ($p=0.003$). Patients receiving ropinirole had a significantly greater reduction in average daily levodopa dose than those receiving placebo (242 mg vs 51 mg; $p<0.001$). The percent reduction in

levodopa dose was also larger in those treated with ropinirole than those treated with placebo (31% vs 6%, respectively; $p<0.001$). Significantly fewer patients treated with ropinirole required reinstitution of levodopa due to worsening Parkinson's disease (23.3% vs 42.6%; $p<0.001$).

Selegiline did not significantly affect the number of patients treated with ropinirole who reached the primary endpoint. More ropinirole patients had improvement in the CGI overall score than those taking placebo (58.5% vs 32.1%; $p<0.002$). Stratification for selegiline use and treatment was significant. Similar percentages of patients taking ropinirole (45.8%) and selegiline were rated as improved as compared with those taking placebo and selegiline (43.3%). In the non-selegiline stratum, significantly more patients taking ropinirole were "improved" (71.7% vs 17.4%; $p=0.002$). Ropinirole patients had a greater reduction in percentage of hours spent in the "off" state during the waking day as compared to placebo (11.7% vs 5.1%; $p=0.039$).

Dyskinesia was the only adverse effect that differed significantly between the ropinirole and placebo groups (33.7% vs 13.0%, respectively; $p=0.006$). However, 43% of the 33.7% of the ropinirole-treated patients who experienced worsening dyskinesias experienced them only during the fixed-dose phase of the trial when no adjustments in the levodopa doses were allowed. When reductions in the levodopa dose were allowed, the dyskinesia stopped.

Adverse Effect

Pramipexole

In patients with early Parkinson's disease the following adverse events were reported more frequently (>5%) in the pramipexole-treated patients: nausea (27.6% for pramipexole vs 17.9% for placebo), dizziness (25.0% vs 24.3%), somnolence (21.9% vs 8.9%), insomnia (17.0% vs 11.5%), constipation (13.7% vs 6.0%), asthenia (13.9% vs 11.5%), and hallucinations (9.0% vs 2.6%).⁷ The side effect profile changes somewhat in patients with advanced disease. In these patients the reported adverse events include: postural hypotension (52.7% vs 48.1%), dyskinesia (47.3% vs 31.4%), extrapyramidal syndrome (27.7% vs 25.8%), insomnia (26.9% vs 21.6%), dizziness (25.8% vs 25.0%), hallucinations (16.5% vs 3.8%), accidental injury (16.5% vs 14.8%), dream abnormalities (10.8% vs 9.5%), constipation (10.0% vs 8.7%), asthenia (10.0% vs 8.0%), and somnolence (8.8% vs 6.1%).⁷

Ropinirole

As with pramipexole, the adverse event profile for ropinirole differs between early and advanced disease.⁸ In patients with early Parkinson's disease not treated with levodopa, adverse events occurring at a rate greater than 10% include nausea (60% for ropinirole vs 22% for placebo), dizziness (40% vs 22%), somnolence (40% vs 6%), vomiting (12% vs 7%),

syncope (12% vs 1%), fatigue (11% vs 4%), dyspepsia (10% vs 5%), and viral infection (11% vs 3%). In patients with advanced Parkinson's disease treated with ropinirole and levodopa, the most common adverse events (>10%) included dyskinesias (34% vs 13%), nausea (30% vs 18%), dizziness (26% vs 16%), somnolence (20% vs 8%), headache (17% vs 12%), hallucinations (10% vs 4%) and falls (10% vs 7%).⁸

Cost, Dose, How Supplied

Pramipexole

Pramipexole is available as 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 1.5 mg tablets. In patients with normal renal function the drug should be started at a dose of 0.125 mg three times daily and increased slowly to a maximum daily dose of 4.5 mg (see Table 1).⁷ Patients should be titrated to a dose that is maximally effective, but balanced with potential side effects.⁷

Table 1. Pramipexole Dose Titration Schedule

Week	Dose	Total Daily Dose
1	0.125 mg three times daily	0.375 mg
2	0.25 mg three times daily	0.75 mg
3	0.5 mg three times daily	1.5 mg
4	0.75 mg three times daily	2.25 mg
5	1 mg three times daily	3 mg
6	1.25 mg three times daily	3.75 mg
7	1.5 mg three times daily	4.5 mg

Pramipexole is primarily eliminated through the kidneys. The dose should be adjusted in patients with renal impairment (see Table 2).⁷

Table 2. Adjusting Pramipexole Based on Creatinine Clearance

Creatine Clearance	Starting Dose (mg)	Maximum Daily Dose (mg)
>60 mL/min	0.125 three times daily	1.5 three times daily
35-59 mL/min	0.125 two times daily	1.5 two times daily
15-34 mL/min	0.125 once daily	1.5 once daily
<15 mL/min	Not studied	Not studied

The average wholesale price (AWP) of pramipexole is \$43.31 for 63 of the 0.125 mg tablets, \$82.13 for 90 of the 0.25 mg tablets and \$164.25 for 90 of the 1 mg and 1.5 mg tablets. The cost for one month of therapy with 1.5 mg three times daily would be \$164.25.¹⁷

Ropinirole

Ropinirole is available as 0.25 mg, 0.5 mg, 1 mg, 2 mg, and 5 mg tablets. The dose should be started at 0.25 mg three times daily and titrated at weekly intervals to a maximum daily dose of 3 mg (see Table 3).⁸ Ropinirole can be taken without regard

to food three times daily. Ingestion of food may reduce the incidence of nausea due to the decreased maximum concentration of ropinirole.⁸ When discontinuing ropinirole, the dose should be tapered over 7 days. Reduce the dose from three times daily to twice daily for 4 days; then reduce to once daily for 3 days before stopping therapy.⁸

Table 3. Ropinirole Dose Titration Schedule

Week	Dose	Total Daily Dose
1	0.25 mg three times daily	0.75 mg
2	0.5 mg three times daily	1.5 mg
3	0.75 mg three times daily	2.25 mg
4	1.0 mg three times daily	3.0 mg

The AWP of ropinirole is \$88.75 for 100 of the 0.25 mg, 0.5 mg, 1 mg and 2 mg tablets. The AWP is \$177.50 for 100 of the 5 mg tablets. The cost for one month of therapy with 1 mg or 2 mg three times daily would be \$79.88.¹⁷

The newer dopamine agents are less expensive than the older drugs, bromocriptine and pergolide. The AWP for generic bromocriptine is \$156.05 for 100 of the 2.5 mg tablets. The cost for one month of therapy with 5 mg three times daily is \$280.89.¹⁷ The AWP for pergolide is \$21.46 for 30 of the 0.05 mg tablets, \$116.82 for 100 of the 0.25 mg tablets, and \$370.23 for 100 of the 1 mg tablets. The cost for one month of therapy with 1 mg three times daily is \$333.21.¹⁷

Conclusion

The ergot alkaloids bromocriptine and pergolide are first generation dopamine agonists indicated as adjuncts to levodopa. Serious adverse events associated with the ergot-derived dopamine agonists are lower limb edema, pleuropulmonary fibrosis, and retroperitoneal fibrosis. Because pramipexole and ropinirole do not contain the ergot chemical structure they are not expected to cause these adverse events. Clinical trials have demonstrated that pramipexole and ropinirole are effective for treatment of Parkinson's disease symptoms both as monotherapy in early disease and as adjuncts to levodopa. Comparative clinical trials have not been conducted comparing pramipexole and ropinirole to the first generation agents. Post-marketing surveillance and future studies are needed to further evaluate the role of the second-generation dopamine agonists. ■

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