Ropinirole therapy for Parkinson’s disease

Rajesh Pahwa, Kelly E Lyons and Robert A Hauser†

Ropinirole (Requip®, GlaxoSmithKline) is a novel nonergoline dopamine D2 agonist indicated for the treatment of early and advanced Parkinson’s disease. It is mainly metabolized by the liver and its elimination half-life is approximately 5.8 h. When used as monotherapy in early Parkinson’s disease, ropinirole improves signs and symptoms of the disorder. When used as an adjunct to levodopa in advanced Parkinson’s disease patients with motor fluctuations, ropinirole reduces ‘off’ time and allows a reduction of levodopa dose. The initial use of ropinirole in early Parkinson’s disease to which levodopa is added when necessary, has been demonstrated to lead to a lower incidence of dyskinesias compared with treatment with levodopa alone. An 18F-dihydroxyphenylalanine positron emission tomography study suggested the possibility that ropinirole could slow the progression of loss of dopamine neurons compared with treatment with levodopa but this remains to be proven. Side effects of ropinirole include nausea, somnolence, edema, orthostatic hypotension, hallucinations and dyskinesia. A once-daily formulation of ropinirole is currently in development that has the potential for greater convenience, improved tolerability and greater efficacy.


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Parkinson’s disease (PD) is a progressive neurodegenerative disorder whose cardinal features include tremor, rigidity and bradykinesia. No treatments have yet been proven to slow the progression of the underlying disease. Currently available medications improve signs and symptoms, reduce physical disability and improve the quality of life of PD patients. There are multiple classes of medications available including levodopa, dopamine agonists, monoamine oxidase B inhibitors, catechol-O-methyltransferase inhibitors, anticholinergics and amantadine (TABLE 1). Symptomatic therapy is usually initiated when a patient’s PD symptoms cause functional disability or social embarrassment. Medications typically provide good control of symptoms for several years but ultimately disability increases. With disease progression, patients may develop imbalance, dementia, other nonmotor problems or motor complications including response fluctuations and dyskinesias [1]. These problems can be more disabling than primary parkinsonian symptoms. No treatments are known to forestall the development of imbalance or dementia. In contrast, initial use of dopamine agonists rather than levodopa has been demonstrated to delay the onset of motor fluctuations and dyskinesias [12]. If motor fluctuations and dyskinesias cannot be adequately managed with medications, deep brain stimulation of the subthalamic nucleus can be helpful [3].

Ropinirole (Requip®, GlaxoSmithKline) is a novel nonergoline dopamine D2 agonist indicated for the treatment of early and advanced PD. In the USA, pramipexole (Mirapex®, Pfizer Inc.) and injectable apomorphine (APOKYN™, Bertek), other nonergoline dopamine agonists and the ergoline dopamine agonists, pergolide (Permax®, Valeant) and bromocriptine, are also available. Cabergoline (Cabaser®, Pfizer Inc.) and lisuride are available outside the USA. Sumanirole and rotigotine transdermal patches are dopamine agonists that are currently under evaluation in clinical trials.
Pharmacology

Ropinirole is a selective dopamine agonist at the D2, 3 and 4 subreceptors [4]. It has nonsignificant actions at D1 and non-dopamine neurotransmitter receptors [5]. Ropinirole binds to both central and peripheral dopamine receptors. It’s action on central dopamine receptors results in an improvement of parkinsonian signs and may also provide neuroprotective effects [6]. The action of ropinirole on peripheral dopamine receptors can lead to nausea or orthostatic hypotension, side effects that can usually be avoided by slow titration of the drug [7].

Pharmacokinetics

In healthy volunteers, ropinirole is rapidly and almost completely absorbed [8]. Less than 10% of the drug is excreted in the urine after oral or intravenous administration [9]. There is a relatively high variability in the pharmacokinetics of ropinirole. The maximum plasma concentration (Cmax) is usually reached in approximately 1.5 h (range: 0.5–4 h) and the elimination half-life is approximately 3 h [8]. In PD patients, the time to reach Cmax is approximately 1.5 h (range: 0.5–6 h) and the elimination half-life is approximately 5.8 h (range: 2–10 h) [10]. Ropinirole is a lipophilic amine and is extensively distributed from the vascular compartment. It has low protein binding that is independent of its plasma concentration [11].

Ropinirole is mainly metabolized by the liver and SmithKline and French (SK & F) 104557 is the main metabolite [9]. Other metabolites include the glucuronide of the metabolite SK & F 89124 and the carboxylic acid metabolite SK & F 97930, neither of these metabolites has any significant pharmacological activity [8]. Hence, all of the pharmacological activity of oral ropinirole is based on the parent molecule. The main enzyme responsible for the metabolism of ropinirole is the cytochrome (CYP) P450 enzyme CYP1A2, with CYP3A making a minor contribution [12]. Pharmacokinetic parameters of ropinirole measured in the fasted state and after a high-fat breakfast suggest that although food reduces the rate of absorption of ropinirole, this is of minimal clinical consequence [13]. In a study of 12 PD patients, the mean Cmax was reduced by 25% following a high-fat breakfast and the median time to maximum concentration was delayed by 2.6 h compared with results obtained in the fasted state [13]. This was accompanied by a small but significant reduction in the area under the curve (13%).

There are no significant effects on the pharmacokinetics of ropinirole on the basis of age, gender, rate of creatinine clearance, PD stage, concurrent illness or use of concomitant medications [8,14]. PD patients older than 65 years show a 15% slower clearance of ropinirole than patients younger than 65 years, and clearance in patients older than 75 years is slower than that observed in patients aged 65 to 75 years. These findings are most likely to be related to slower rates of hepatic metabolism of the drug due to aging. These age-related differences are unlikely to be of clinical consequence as the medication is titrated to clinical effect. There are no significant differences in the clearance of ropinirole between men and women who are not taking hormone replacement therapy [14]. In women taking hormone replacement therapy, there was a significant reduction in the clearance of ropinirole which resulted in an increase in elimination half-life of ropinirole to 9 h.

In patients with creatinine clearance in the range of 30–177 ml/min, there were no significant differences in the clearance of ropinirole [8]. As the excretion of ropinirole is mainly nonrenal, no dose adjustments are necessary for patients with mild-to-moderate renal impairment. No pharmacokinetic studies have been performed in patients with severe renal impairment. As ropinirole is mainly metabolized by the liver, the use of ropinirole is not recommended in patients with significant hepatic impairment.

Ropinirole is mainly metabolized by the CYP1A2 enzyme system and it is possible that ropinirole could interact with other drugs that are cleared by or are inhibitors or inducers of this enzyme [15]. Ciprofloxacin is a powerful inhibitor of CYP1A2 and does affect the pharmacokinetics of ropinirole. In a study of 12 PD patients, coadministration of ropinirole and ciprofloxacin increased the Cmax of ropinirole by 60% and the area under the curve by 84%. Hence it is important to consider adjusting the dose of ropinirole if drugs known to inhibit CYP1A2 are either introduced or withdrawn.

There are no differences in the rates of absorption or availability of ropinirole with or without levodopa. Similarly, there are no significant differences in the absorption, availability or elimination half-life of levodopa when administered with ropinirole [8]. Selegiline, amantadine, tricyclic antidepressants, benzodiazepines, ibuprofen, thiazides, anticholinergics and antihistamines have no effect on the clearance of ropinirole [8].

Table 1. Different medications currently available for Parkinson’s disease.

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Name</th>
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<tr>
<td>Levodopa</td>
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<td>Pramipexole (Mirapex®)</td>
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<td>Apomorphine (APOKYN™)</td>
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<td>Pergolide (Permax®)</td>
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<td>Monoamine oxidase B inhibitors</td>
<td>Selegiline (Eldepryl®)</td>
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<td>Catechol-O methyl-transferase inhibitors</td>
<td>Entacapone (Comtan®)</td>
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<td>Tolcapone (Tasmar®)</td>
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<td>N-methyl D-aspartate antagonists</td>
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<td>Anticholinergics</td>
<td>Trihexyphenidyl (Artane®)</td>
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Preclinical studies
Ropinirole causes biphasic spontaneous locomotor activity and contralateral circling in 6-hydroxodopamine-lesioned mice [5]. In marmosets made parkinsonian with the dopamine neuron toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), ropinirole improved all motor and behavioral deficits. This response started 10–20 min after dosing and exceeded 2 h. No tolerance was seen following chronic administration [5]. The effects of bromocriptine and ropinirole were compared in a group of MPTP-treated common marmosets [16]. Both bromocriptine and ropinirole improved parkinsonian signs. However, ropinirole had a more rapid onset of anti-parkinsonian activity and a potency more than five-times greater than that of bromocriptine. The combination of ropinirole and levodopa increased the effectiveness seen with either ropinirole or levodopa alone and produced a more marked additive effect on motor activity than bromocriptine and levodopa.

Pearce and colleagues compared the ability of ropinirole, bromocriptine and levodopa to induce dyskinesia in MPTP-treated common marmosets [17]. Animals were treated with placebo, ropinirole, bromocriptine, or levodopa/carbidopa daily for 30 days (n = 4 per group). The drugs were titrated to provide similar improvement in motor disability. Levodopa rapidly induced dyskinesia of moderate-to-severe intensity, whereas ropinirole and bromocriptine produced only mild dyskinesia over the period of the study. This study suggested the possibility that in treating PD patients, the initial use of dopamine agonists may cause less development of dyskinesia as compared with initial treatment with levodopa. In a separate group of marmosets previously treated with levodopa to cause dyskinesia (levodopa-primed), ropinirole caused severe dyskinesia comparable with that induced by levodopa. This latter study suggests that once dyskinesias are established, either levodopa or dopamine agonists are able to bring it out. In clinical practice this may be seen as an increase in dyskinesia when a dopamine agonist is added in patients who are already experiencing dyskinesia on levodopa.

Clinical efficacy studies
Ropinirole as monotherapy
There have been a number of studies that have evaluated the efficacy of ropinirole as monotherapy in the treatment of PD [1,18–20]. These include two placebo-controlled studies and one bromocriptine controlled study [18–20]. Adler and colleagues reported the results of a prospective, randomized, placebo-controlled, double-blind, parallel-group, 6-month study to assess the efficacy and safety of ropinirole in early PD patients [18]. In this study, 241 de novo PD patients of Hoehn and Yahr Stages I to III were randomized to ropinirole (n = 116) or placebo (n = 125). Ropinirole was titrated to at least 1.5 mg three-times daily (maximum dose 8 mg three-times daily). The primary efficacy end point was the percentage improvement in Unified Parkinson’s Disease Rating Scale (UPDRS) motor score. The ropinirole-treated group improved by 24% compared with a 3% worsening in the placebo-treated group (p < 0.001).

Ropinirole and levodopa to induce dyskinesia in MPTP-treated common marmosets [17]. Animals were treated with placebo, randomized, placebo-controlled, double-blind, parallel-group, motor activity than bromocriptine and levodopa.

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Ropinirole as add-on therapy to levodopa
Rascol and colleagues [21], and Lieberman and colleagues [22] evaluated ropinirole as add-on therapy in advanced PD. Rascol and colleagues reported 46 PD patients with motor fluctuations on levodopa who were randomized to the addition of ropinirole or placebo in a 3-month controlled trial. In this study, ropinirole was administered twice-daily rather than the usual three-times daily. Ropinirole decreased off time by 44% (from 47% at baseline to 27% at end point) while placebo reduced off time by 24% (from 44% at baseline to 34% at end point; p = 0.085). Per the Clinician’s Global Assessment, 76% of ropinirole-treated patients improved compared with 35% of the placebo-treated patients (p = 0.004).

Lieberman and colleagues also evaluated the adjunctive use of ropinirole in PD patients with motor fluctuations on levodopa [22]. This was a 6-month double-blind, placebo-controlled study in which patients were randomized to the addition of ropinirole (n = 95) or placebo (n = 54). The levodopa dose was then reduced in a proscribed manner. The primary end point was the number of patients who achieved a 20% or greater decrease in levodopa dose and a 20% or greater reduction in the percentage of off time between baseline and final visit using patient diaries. Overall, 35% of ropinirole-treated patients and 13% of the placebo-treated patients met the primary end point definition (p < 0.003). The mean daily dose of levodopa was reduced by 242 mg in the ropinirole group and by 51 mg in the placebo group (p < 0.001). Off time was reduced by 11.7% in the ropinirole group and 5.1% in the placebo group (p = 0.039).
Thus, the use of ropinirole as an adjunct to levodopa in advanced PD patients with motor fluctuations, reduces off time and allows a reduction of levodopa dose.

**Use of ropinirole to delay the onset of motor complications**

The use of ropinirole rather than levodopa, when symptomatic therapy is first required, has been shown to delay the onset of motor fluctuations and dyskinesias [1,20,23]. Rascol and colleagues conducted a 5-year study in 268 de novo PD patients in a randomized, double-blind, parallel group design [1]. The study evaluated initial treatment with ropinirole compared with levodopa to which open-label levodopa could be added as necessary. The primary outcome measure was the time to onset of dyskinesia. The mean daily doses of ropinirole at the end of the study were 16.5 mg of ropinirole (plus 427 mg of levodopa) in the ropinirole group and 753 mg of levodopa in the levodopa group. In the ropinirole group, 29 of the 85 patients (3%) did not require levodopa supplementation. The analysis of time to dyskinesia significantly favored ropinirole (p < 0.001) and at 5 years the cumulative incidence of dyskinesia was 20% in the ropinirole group and 45% in the levodopa group. Disabling dyskinesias were also less frequent in the ropinirole group (hazard ratio for remaining free of disabling dyskinesia: 3.02; 95% confidence interval 1.52–6.02; p = 0.002) and 8% of patients in the ropinirole group and 23% in the levodopa group developed disabling dyskinesia during the study. Wearing-off was also less frequent with ropinirole than levodopa, however, freezing of gait was more often seen in the ropinirole group. For patients who completed the study, the difference in change in motor UPDRS scores was significant in favor of levodopa (4.48 points; p = 0.008). The difference in change in UPDRS ADL scores favored ropinirole but was not significant (1.53 points; p = 0.08).

Whone and colleagues conducted a 2-year randomized, double-blind prospective study in which a secondary end point of the study was the occurrence of dyskinesia [23]. Patients with early PD were randomized to treatment with ropinirole or levodopa to which open-label levodopa could be added. At 2 years, mean medication doses were 12.3 mg for ropinirole and 559 mg for levodopa. Supplementary levodopa was required in 15 out of 87 ropinirole-treated patients and seven out of 75 levodopa-treated patients. Motor scores were more improved in the levodopa group but Clinical Global Improvement scores were similar across groups. After 2 years of follow-up, only 3% of the patients in the ropinirole group developed dyskinesia compared with 27% in the levodopa group (p < 0.001).

In their 3-year randomized double-blind parallel group study comparing ropinirole and bromocriptine, Korczyn and colleagues used time to onset of dyskinesia as a secondary end point [20]. Dyskinesia developed only in a minority of patients in both groups. At the end of the study, only 7.7% patients in the ropinirole group and 7.2% of the bromocriptine-treated patients developed dyskinesia (p = 0.84).

Thus, early use of ropinirole monotherapy in patients with early PD to which levodopa is added when necessary reduces the risk of dyskinesia at 5 years. However, the functional impact of such benefit is not yet clear. It appears a reasonable presumption that mild dyskinesia in early disease is a predictor of more severe dyskinesia in later disease but this has not yet been proven. Nonetheless, even within 5 years, disabling dyskinesia is less common with initial ropinirole treatment compared with levodopa. Another consideration is that improvement in parkinsonian motor features as measured by UPDRS scores is greater with levodopa. However, it can be argued that the ropinirole patients in these studies were adequately treated since the investigators could add or increase open-label levodopa at any time. Longer term studies that focus on overall patient well-being as the disease progresses may be required to answer many of these remaining questions.

**Effect of ropinirole on disease progression**

Prediagnostic studies have demonstrated that dopamine agonists scavenge free radicals and show a neuroprotective effect in vitro [24]. A pilot clinical study using 18-F-dopa positron emission tomography (PET) suggested that PET could be used to measure the progression of PD [25]. Based on this pilot study, a prospective, 2-year, randomized, double-blind, study was conducted to compare the rates of loss of dopamine-terminal function as assessed by PET in patients with early PD, randomized to receive either ropinirole or levodopa, to which supplementary levodopa could be added as necessary. The primary outcome measure was reduction in putamen fluorodopa uptake between baseline and 2 years. At the end of the study, the percentage decrease from baseline in putaminal 18-F-DOPA uptake was significantly less in the ropinirole group (-14%) compared with the levodopa group (-23%; p < 0.01). Such a result is potentially consistent with other studies and may reflect a slowing of disease progression. However, pharmacologic or compensatory effects of the medications on dopamine neurons as imaged by PET cannot be excluded. In addition, there was no placebo group, making the interpretation of the results difficult. Hence, there are currently no conclusive data to demonstrate that ropinirole provides neuroprotective effects in PD. This remains an area of great interest but methodological limitations in our ability to measure progression of the underlying disease must be overcome.

**Adverse effects**

The clinical safety of ropinirole is similar to other dopamine agonists. Most side effects are related to its dopaminergic activity. Adverse effects reported in more than 5% of PD patients in clinical trials of early disease included nausea, dizziness, somnolence, headache, vomiting, syncope, fatigue, dyspepsia, constipation, pain, increased sweating, asthenia, pedal edema, orthostatic symptoms, abdominopelvic pain, confusion, hallucinations and abnormal vision [26]. Similarly, the most commonly reported adverse effects (>5%), in PD patients with advanced disease (with levodopa) included dyskinesia, nausea, dizziness, worsening of parkinsonism, somnolence, headache, insomnia, hallucinations, falls, abdominopelvic pain, confusion, increased sweating, vomiting, arthralgia, tremor, anxiety, constipation, dry mouth and paresthesia [26].
In the 5-year levodopa controlled study, most of the adverse effects were similar in the ropinirole and levodopa groups [1]. However, somnolence occurred in 27% of patients in the ropinirole group as compared with 19% of patients in the levodopa group, hallucinations 17 versus 6% and edema of the legs 14 versus 6%. Adverse events that were seen more frequently with levodopa included dyskinesia 26 versus 9%, depression 23 versus 15%, and increased sweating 10 versus 6%.

There are concerns that patients on dopamine agonists may have episodes of sudden irresistible sleep attacks and several case reports have been published regarding patients on ropinirole or pramipexole [27]. However, similar episodes have also been described with other antiparkinsonian medications including levodopa [28,29]. Somnolence, as an adverse event, has been reported more frequently with ropinirole than placebo or levodopa in randomized clinical trials [1,18]. However, the risk of somnolence is not greater with ropinirole than with other dopamine agonists [30]. In clinical practice it is prudent to question patients on antiparkinsonian therapy on sleepiness and unintended sleep episodes.

It is believed that the long-term use of nonergot dopamine agonists such as ropinirole will not cause pulmonary, retroperitoneal or cardiac valvular fibrosis reported with the ergot dopamine agonists [31,32]. Some case reports suggest that this may be the case but long-term postmarketing surveillance is still lacking [33].

**Movement Disorder Society & American Academy of Neurology ropinirole guidelines**

The Movement Disorder Society commissioned a task force to develop an evidence-based review on the management of PD [34]. According to this review, there is sufficient evidence to conclude that ropinirole is clinically useful in the management of early PD and in PD with motor fluctuations. They agreed that the early use of ropinirole (to which levodopa is added when clinically needed) reduces the risk of dyskinesia over 5 years. They concluded that in patients with early PD, the reported superior efficacy of levodopa over ropinirole was marginal and the clinical relevance of this difference was unclear.

The American Academy of Neurology report on the practice parameters for initiating treatment of PD concluded that levodopa and ropinirole were effective in improving motor and activities of daily living functions in PD patients requiring dopaminergic therapy [35]. However, the report concluded that levodopa was more effective than ropinirole in treating motor and ADL features of PD. They recommended that in patients who require initiation of dopaminergic therapy, either levodopa or a dopamine agonist, such as ropinirole could be used.

**Ropinirole for restless legs syndrome**

Restless legs syndrome (RLS) is a common disorder in the general population and may also be seen in PD patients. It is associated with a desire to move the extremities, often associated with paresthesias or dysesthesias, worsening of symptoms at rest with at least temporary relief by activity and worsening of symptoms in the evening or night.

Ropinirole appears to be effective in the management of RLS. Ondo and colleagues reported the use of ropinirole in 16 patients with RLS in an open-label trial [36]. The mean daily dose was 2.8 mg/day. The 13 patients who completed the study had a 58.7% improvement in the abbreviated International Restless Legs Study Group questionnaire. Saletu and colleagues investigated the acute effects of ropinirole 0.5 mg versus placebo in 12 untreated RLS patients using polysomnography studies [37]. Ropinirole significantly improved periodic leg movements in sleep associated with RLS and objective and subjective sleep quality measures improved. Ropinirole also increased the total sleep time and sleep efficacy as compared with placebo [38]. Trenkwalder and colleagues conducted a 12-week, prospective, double-blind, randomized comparison of 284 patients with RLS treated with ropinirole versus placebo [39]. There was a significant improvement in the International Restless Legs Scale in the ropinirole group (mean dose 1.9 mg/day) compared with placebo. Of the patients on ropinirole, 53% showed improvement in the Clinical Global Impression Scale compared with 41% of patients on placebo. Ropinirole also resulted in significantly greater improvements in sleep and quality of life end points. The most common adverse events were nausea and headache. Finally, Adler and colleagues conducted a double-blind, placebo-controlled, crossover study of 22 RLS patients receiving a maximum dose of ropinirole of 6 mg/day for a 4-week period [40]. The average dose of ropinirole was 4.6 mg/day with 14 patients taking the maximum 6 mg/day. There was approximately a 50% improvement in RLS according to the RLS rating scale and patient diaries. Of 22 patients, eight had complete resolution of their RLS. The most common side effects were dizziness and nausea.

**Ropinirole controlled release**

GlaxoSmithKline, in partnership with Skye Pharma, is currently investigating a once-daily formulation of ropinirole, although no published information is yet available. The most obvious advantage of such a formulation is the convenience of only taking one dose per day. This benefit would be greatest for patients with early PD who could be managed on ropinirole monotherapy, before they require medications, such as levodopa that are taken several times per day. There is also the potential for better tolerability and perhaps greater efficacy (particularly if higher daily doses are well-tolerated), although this is currently unproven. In addition, it is possible that a highly effective once-daily formulation could provide an even greater capacity to forestall the development of motor fluctuations and dyskinesias when used as initial therapy. This formulation may provide even more stable, physiologic dopamine receptor stimulation (continuous dopaminergic stimulation) that is thought to be important in avoiding the emergence of motor complications.

**Expert opinion & five-year view**

Ropinirole has been demonstrated to be safe and effective to improve the signs and symptoms of PD as monotherapy in...
early disease and as an adjunct to levodopa in advanced disease. Studies have demonstrated that the initial use of ropinirole, to which levodopa is added when necessary, causes less motor fluctuations and dyskinesias than treatment with levodopa alone. Although this strategy has been widely adopted, there remains some debate. First, patients treated with levodopa alone experienced a greater improvement in parkinsonian signs than those treated with ropinirole to which levodopa could be added. This result was surprising and has not been fully explained. However, it can be argued that this difference was not clinically significant since investigators could always have added more levodopa if parkinsonian signs were not well controlled. Second, the studies were only up to 5 years in duration and neither strategy was definitively demonstrated to be superior overall. It appears a reasonable presumption that the onset of any dyskinesia in the first 5 years would predict worse dyskinesia in subsequent years that could have an increasingly negative impact on patient function and would also limit the clinician’s ability to increase medications to overcome worsening parkinsonian symptoms but this has yet to be proven. Of note, in the 5-year study, disabling dyskinesia was observed more frequently with levodopa alone. We favor the initial use of a dopamine agonist, such as ropinirole in younger patients (<70 years old) as they are at higher risk of developing dyskinesia and have a longer treatment horizon than older patients. They also tend to tolerate dopamine agonists better than older individuals. However, Shulman and colleagues have demonstrated with a retrospective chart review that five out of 16 patients (31%) over 80 years of age had successful treatment with ropinirole. It was concluded that ropinirole use may be warranted in a selected group of elderly patients. It would be of great value to have very long-term studies that evaluate overall status and functional outcome, but high cost and feasibility issues may make such studies difficult to undertake.

The possibility that ropinirole and other dopamine agonists can slow loss of dopamine neuron function remains of great interest. To evaluate this possibility requires better ways to monitor disease progression. If imaging studies are to be used, we need to know more on the pharmacologic and compensatory mechanisms that medications could effect which would interfere with our ability to interpret these studies. Comparisons with placebo and levodopa would be helpful.

Over the next few years, the potential benefits of a once-daily ropinirole formulation will be studied. It is likely that such a formulation will be at least as effective as standard ropinirole and will offer greater convenience, particularly for patients on ropinirole monotherapy. It is possible that it could provide greater tolerability and may make introduction and escalation easier. It may also allow higher daily doses that could provide greater efficacy. Moreover, the controlled release formulation may provide more physiologic continuous dopaminergic stimulation and further delay the need for levodopa therapy. Taken together, these factors could forestall motor fluctuations and dyskinesias even more. A very long-term study comparing the initial use of ropinirole controlled release to which levodopa could be added to levodopa alone and evaluating overall status, would be of great value.

Key issues

- Parkinson’s disease (PD) is a progressive neurological disorder for which no treatment has yet been proven to slow progression.
- Ropinirole is a nonergoline dopamine agonist that has been demonstrated to be safe and effective to treat signs and symptoms of PD. It is approved in the USA as monotherapy in early PD and as an adjunct to levodopa in advanced disease.
- Early use of ropinirole, to which levodopa can be added, is associated with a lower incidence of development of dyskinesias than treatment with levodopa alone.
- There is interest as to whether ropinirole is able to slow the loss of dopamine neuron function over time.
- Clinical studies have demonstrated that ropinirole is also effective to treat restless legs syndrome.
- A once-daily formulation of ropinirole is currently being investigated.

References

Papers of special note have been highlighted as:
• of interest
• of considerable interest


- One of the few randomized studies comparing the safety and efficacy of two dopamine agonists.


- Examines the progression of disease in patients randomly assigned to ropinirole or levodopa using positron emission tomography imaging as a marker.


- Represents the official practice parameters of the American Academy of Neurology for the initiation of treatment for Parkinson's disease using an evidence-based approach.


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A large multicenter, randomized trial examining the use of ropinirole for restless legs syndrome.


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