REVIEW ARTICLE

Ropinirole Versus Levodopa: Better Clinical Benefits in Parkinson's Disease

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Abstract

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Although PD can develop at any age, it begins most commonly in older adults, with a peak age at the onset of around 60 years. Levodopa and dopamine agonists such as ropinirole are used in Parkinson's treatment. This complete literature search was done using Google Scholar and PubMed. This review is to compare the safety and efficacy of ropinirole with that of Levodopa.

Keywords: Parkinson's disease, Ropinirole, Levodopa, Unified Parkinson's Disease Rating Scale (UPDRS), A Dopamine agonist.

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Introduction

Parkinson's Disease

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system.[1]

Parkinson's disease (PD) vs. parkinsonism

Parkinsonism is defined by any combination of six specific, non-overlapping, motoric features, so-called cardinal features: tremor-at-rest, bradykinesia, rigidity, loss of postural reflexes, flexed posture and the ''freezing'' phenomenon (where the feet are transiently ''glued'' to the ground).[1]

Not all six of these cardinal features need be present, but at least two should be before the diagnosis of parkinsonism is made, with at least one of them being tremor-at-rest or bradykinesia.[1]

Classification

Classification of the parkinsonian states

- Primary parkinsonism (Parkinson's disease) Sporadic Known genetic etiologies
- Secondary parkinsonism (environmental aetiology)[2]

A. Drugs

- Dopamine receptor blockers (most commonly antipsychotic medications)
- Dopamine storage depletors (reserpine)

B. Postencephalitic
C. Toxins – Mn, CO, MPTP, cyanide
D. Vascular
E. Brain tumours
F. Head trauma
G. Normal pressure hydrocephalus

- Parkinsonism-Plus Syndromes

A. Progressive supranuclear palsy
B. Multiple system atrophy
C. Cortical-basal ganglionic degeneration

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D. Parkinson-dementia-ALS complex of Guam
E. Progressive pallidal atrophy
F. Diffuse Lewy body disease (DLBD)

- Heredodegenerative disorders

A. Alzheimer disease
B. Wilson disease
C. Huntington disease
D. Frontotemporal dementia on chromosome 17q21
E. X-linked dystonia-parkinsonism (in Filipino men; known as lubag)

- Levodopa is usually the most effective on average of all the drugs for symptoms of PD, especially for bradykinesia or rigidity (class I, II, III) (Table 1).[43]
- Anticholinergic agents are commonly used as initial therapy, especially in cases where the tremor is predominant, but there is evidence that anticholinergic agents are better than levodopa for tremors (class II).[43]
- Amantadine has a modest effect on all features of the disease and has a low adverse effect profile (class II).[43]
- Dopamine agonists are effective for all features of the disease, but are not generally as effective as levodopa and are more expensive than levodopa (class I, II).[43]
- Selegiline. Class I evidence suggests a mild therapeutic and

Table 1: Levels of evidence employed in 1993

Class I	Evidence is provided by one or more well-designed, randomized, controlled clinical trials.
Class II	Evidence is provided by one or more well-designed clinical studies such as case-control, cohort studies, etc.
Class III	Evidence provided by expert opinion, nonrandomized historical controls or case reports of one or more.

partial protective effect from selegiline, but confirmation of the neuroprotective effect is needed. Selegiline also has an antidepressant activity that offers modest direct symptomatic benefit for PD (Evidence not classified in the statement).[43]

- Current levels of evidence can be seen in Table 2

Clinical description of Parkinson's disease

Although non-motor symptoms (e.g., constipation, aching shoulder, hypo-osmium, depression) may begin before the motor features of PD, these non-motor symptoms are too common in the general population to lead to a diagnosis of PD on their own. The motor symptoms of PD begin insidiously and gradually worsen. Symptoms, such as rest tremors, can be intermittent at the onset being present only in stressful situations. Symptoms tend to worsen on one side of the body before spreading to involve the other side:[2]

Epidemiology of Parkinson's disease

- Although PD can develop at any age, it begins most common in older adults, with a peak age at the onset of around 60 years.
- A positive family history doubles the risk of developing PD to about 4%.[2]

Bradykinesia

- Bradykinesia refers to slowness of movement and is the most characteristic clinical feature of PD, although it may also be seen in other disorders, including depression.
- Bradykinesia is a hallmark of basal ganglia disorders, and it encompasses difficulties with planning, initiating and executing movement and performing sequential and simultaneous tasks.[5]
- The initial manifestation is often slowness in performing activities of daily living and slow movement and reaction times.[6,7] This may include difficulties with tasks requiring fine motor control (eg, buttoning, and using utensils).
- In common with other parkinsonian symptoms, bradykinesia depends on the patient's emotional state. For example, immobile patients who become excited may be able to make quick movements such as catching a ball.
- It is hypothesised that bradykinesia is the result of a disruption in normal motor cortex activity mediated by reduced dopaminergic function. In a study assessing recordings from single cortical neurons in rats with haloperidol-induced bradykinesia, a decrease in firing rates correlated with bradykinesia.[8] Functional neuroimaging studies also suggest impairment in the recruitment of cortical and subcortical systems that regulate kinematic parameters of movement (eg, velocity).[9]
- Because patients with PD have decreased electromyographic activity,[5] they need a series of multiple agonist bursts to accomplish larger movements.[4]

Tremor

- Rest tremor is the most common and easily recognised symptom of PD.[4]
- Tremors are unilateral, occur at a frequency between 4 and 6 Hz, and are almost always prominent in an extremity's distal part. Hand tremors are described as supination–pronation (''pill-rolling'') tremors that spread from one hand to the other.[4]
- Rest tremor in patients with PD can also involve the lips, chin, jaw and legs but rarely involves the neck/head or voice, unlike essential tremor.[4]
- Characteristically, rest tremor disappears with action and during sleep. Some patients also report an ''internal'' shaking that is not associated with a visible tremor.[4][10]

Rigidity

- Rigidity is characterised by increased resistance, usually accompanied by the ''cogwheel'' phenomenon, particularly when associated with an underlying tremor, present throughout the range of passive movement of a limb (flexion, extension or rotation about a joint). It may occur proximally (eg, neck, shoulders, hips) and distally (eg, wrists, ankles). Reinforcing manoeuvres (eg, voluntary movements of the contralateral limb), known as the Froment's manoeuvre,[11] usually increase rigidity and are particularly useful in detecting mild cases of rigidity.[4]
- Rigidity may be associated with pain, and a painful shoulder is one of the most frequent initial manifestations of PD although it is commonly misdiagnosed as arthritis, bursitis or rotator cuff injury.[12][13][4]

Postural deformities

- In addition, the rigidity of the neck and trunk (axial rigidity) may occur, resulting in abnormal axial postures (eg, anterocollis, scoliosis).
- Postural deformities resulting in flexed neck and trunk posture and flexed elbows and knees are often associated with rigidity.
- Striatal limb deformities (eg, striatal hand, striatal toe) may also develop in some patients.
- Other skeletal abnormalities include extreme neck flexion (''dropped head'' or ''bent spine''), truncal flexion (camphormia) and scoliosis.[14,15-17] Camptocormia is characterised by extreme thoracolumbar spine flexion.[4]

Freezing

- Freezing also referred to as motor blocks, is a form of akinesia (loss of movement) and is one of the most disabling symptoms of PD.[18]

- 3 Freezing most commonly affects the legs during walking, but the arms and eyelids can also be involved.[19] It typically manifests as a sudden and transient (usually,10 s) inability to move.
- Five subtypes of freezing have been described: start hesitation, turn hesitation, hesitation in tight quarters, destination hesitation and open space hesitation.[20,4]

Ropinirole

Ropinirole is a non-ergoline dopamine agonist with preferential affinity for the D2-like (D2, 3, 4) receptors. It has the highest affinity at the D3 receptors which are concentrated in the limbic areas of the brain and may account for some of the neuropsychiatric effects.[21]

Ropinirole is regarded as a highly effective agent in treating the signs and symptoms of PD. While it is assumed that the long-acting compound will offer similar efficacy, the decreased pill burden and once-daily therapy may improve patient compliance and as a result, provide additional symptomatic benefits.[21]

Mode Of Action

Ropinirole has a high affinity for and stimulates the post-synaptic dopamine receptors D2 in the central and peripheral nervous systems. The dopamine receptors (D2) are g-protein-coupled inhibitory neurons predominantly in the striatonigral, mesolimbic, and tuberoinfundibular systems. They inhibit adenylyl cyclase and calcium (Ca2+) channels and activate potassium channels leading to their physiological functions.[22-24]

Levodopa

Levodopa is an amino acid that is absorbed from the small bowel and subsequently transported by the neutral amino acid transport system across the blood-brain barrier into the brain where it is decarboxylated to form dopamine.
Other neutral amino acids in the gut and plasma compete for transport.

Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its systemic conversion to dopamine, and nausea and vomiting that can occur from activation of dopamine receptors in the area postrema. This part of the medulla is not protected by a blood-brain barrier.

Levodopa is the single most effective drug for the symptomatic treatment of PD. Its use is associated with decreased morbidity and mortality,[30] and virtually all patients with PD experience a clinically significant benefit.[28,29]

Mode Of Action

Degeneration of the substantia nigra occurs in patients with Parkinson's disease. This condition results in the disruption of the nigrostriatal pathway and thus decreases the striatal dopamine levels. Unlike dopamine, levodopa can cross the blood-brain barrier (BBB). Levodopa converts to dopamine in both the CNS and periphery.[26] To increase the bioavailability of levodopa and decrease its side effects, it is often administered in combination with peripheral decarboxylase inhibitors (such as carbidopa and benserazide). Dopamine decarboxylase inhibitors prevent the conversion of levodopa to dopamine in the periphery, allowing for more levodopa

Table 2: Current levels of evidence classification[43]

Rating of recommendation	*Translation of evidence to recommendations*	*Rating of therapeutic article*
A = Established as effective, ineffective or harmful for the given condition in the specified population	Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies	Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) is/are clearly defined b) exclusion/inclusion criteria are clearly defined c) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is an appropriate statistical adjustment for differences.
B = Probably effective, ineffective or harmful for the given condition in the specified population	Level B rating requires at least one convincing class II study or at least three consistent class III studies	Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR an RCT in a representative population that lacks one criteria a through d.
C = Possibly effective, ineffective or harmful for the given condition in the specified population	Level C rating requires at least two convincing and consistent class III studies	Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
U = Data inadequate or conflicting; given current knowledge, treatment is unproven		Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

to cross the BBB. Once converted to dopamine, it activates postsynaptic dopaminergic receptors and compensates for the decrease in endogenous dopamine.[25,27]

Findings

Randomized, double-blind, placebo-controlled, parallel-group, multicenter study, conducted in 20 centres in China between February 2010 and September 2011, comparing the efficacy of 6 months' treatment with ropinirole PR as adjunctive therapy to L-dopa in subjects with PD not optimally controlled on L-dope centres a.[31]

A total of 347 subjects were randomized and 345 subjects (safety population) received at least one dose of ropinirole PR Z. Zhang et al. / Parkinsonism and Related Disorders 19 (2013) 1022e1026 1023(N =175) or placebo (N=146) Tshe ITT population comprised 344 subjects: ropinirole PR (N=175), placebo (N =169). The PP population comprised a total of 309 subjects: ropinirole PR (N =166), and placebo (N= 143). One subject each in the ropinirole PR and placebo groups was not dosed after randomization and was excluded from the safety population.[31]

There was a larger decrease in the daily dose of L-dopa in the ropinirole PR group than in placebo: at week 24 the mean dosage of L-dopa decreased by 94 or 115.7 mg/day in the ropinirole PR group compared with 34 66.0 mg/day in the placebo group.[31]

The efficacy of adding to L-dopa therapy 6 months of treatment with ropinirole PR or placebo was assessed in Chinese subjects with PD not optimally controlled on L-dopa alone. This was the first evaluation of ropinirole PR in Chinese subjects with PD. Ropinirole PR was more effective in reducing "off" time than placebo, accompanied by an increase in time "on" and time "on" without troublesome dyskinesia.[31]

Ropinirole has also shown promise as an adjunct to levodopa in advanced PD with wearing-off and dyskinesia. A multicentre double-blind, placebo-controlled parallel, the 6-month study reported on 149 parkinsonian patients (Hoehn & Yahr stage II to IV).[32,34]

Of these, 35% of the ropinirole and 13% of the placebo-treated patients achieved the primary end-points, having a 20% or greater reduction in 'off' time and a decrease in the dose of levodopa between baseline and final visit.[34]

The addition of a dopamine agonist such as pergolide, ropinirole, pramipexole, or cabergoline to levodopa in patients with motor complications can reduce ''off'' time by about 1.1 to 1.5 hours per day.[35]

Summary of findings can be seen in Table 3

Ropinirole has been compared to placebo, levodopa, and bromocriptine in separate trials in early Parkinson's disease patients. It has been shown to provide significant improvement vs. placebo on motor function in a 12-week study involving 62 patients.[40] This was a prospective, randomized, double-blind, parallel-group trial in patients with limited or no prior dopaminergic therapy. The dose ranged from 0.5 mg to 5 mg bid. Significantly more ropinirole-treated patients (71% vs. 41% of placebo-treated patients) achieved at least 30% improvement in the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS).[39,41]

In a 6-month interim analysis of a 5-year, randomized, double-blind study of ropinirole vs. levodopa in early Parkinson's patients, Rascol et al.[42] demonstrated ropinirole to be as effective as levodopa in mildly disabled patients.[39]

The study of ropinirole versus levodopa by *Rascol et al.* found that for patients who completed the study (5 years), levodopa treatment resulted in a significantly greater increase in motor improvement than did ropinirole treatment (part III UPDRS, levodopa 4.8 point improvement, ropinirole 0.8 point improvement, *p* 0.008). They also reported that there was no significant difference between the treatment groups at 5 years in the score on the ADL portion of the UPDRS (part II, UPDRS, 1.6 points for ropinirole, 0.0 point change for LD, *p* 0.08).

These results suggest that for the course of the study, levodopa produced more motor improvement than ropinirole.[43]

Dopamine agonists have been shown in various studies to delay the onset of motor complications when used as monotherapy and/or to diminish them when used in dyskinetic patients.[44-49] Dopamine agonists have a longer half-life than levodopa and act directly on the dopamine receptors.[45]

In a five-year study on early Parkinson's disease, ropinirole was found to be effective with a reduced risk of dyskinesia when used alone or with supplemental levodopa.[44,45]

Studies have shown that ropinirole is effective when used as monotherapy in early Parkinson's disease, providing symptomatic relief for up to 5 years.[44,51-53] It is also effective as an adjunct therapy in patients with motor fluctuations: 65% of patients taking ropinirole with levodopa had a 30% increase in "on" time compared with 39% in the placebo group ($p < 0.046$).[54]A recent 6-month study in patients with motor fluctuations showed that the use of ropinirole permits a >20% reduction in levodopa dose, while significantly reducing the time spent "oV" compared with placebo (35% *v* 13%; p=0.003).[50,32]

The results of a 5-year, double-blind, randomised trial comparing ropinirole with levodopa plus benserazide in the treatment of 268 patients with early Parkinson's disease have been recently presented.[44,42] Forty-seven per cent of ropinirole patients and 51% of levodopa patients completed the 5-year study; 34% of patients on ropinirole did so on monotherapy. In those patients on ropinirole who were given levodopa supplements, a lower dose of levodopa was required compared with patients on levodopa alone (427 mg/day *v* 753 mg/day, respectively).

Similar clinical efficacy of treatment in the ropinirole and levodopa groups was demonstrated throughout the study (assessed by change in ADL score). Ropinirole monotherapy was also found to be associated with a significantly lower incidence of dyskinesia than levodopa monotherapy (5% *v* 36% respectively; $p < 0.0001$).

Table 3: Summary of findings

Study	*Design*	*Title*	*Sample Size*	*Conclusion*
Z. Zhang et al.[31]	randomized, double-blind, placebo-controlled, parallel-group multicenter study	Comparing the efficacy of 6 months' treatment with ropinirole PR as adjunctive therapy to L-dopa in subjects with PD not optimally controlled on L-dope centres a.	The PP population comprised a total of 309 subjects: ropinirole PR (N =166), placebo (N= 143). One subject each in the ropinirole PR and placebo groups was not dosed after randomization and was excluded from the safety population.	Ropinirole PR was more effective in reducing "off" time than placebo, accompanied by an increase in time "on" and time "on" without troublesome dyskinesia.
Deleu, D., Northway, M. G., & Hanssens, Y.[34]	A multicentre double-blind, placebo-controlled parallel.	Ropinirole has also shown promise as an adjunct to levodopa in advanced PD with wearing-off and dyskinesia.	the 6-month study reported 149 parkinsonian patients.	35% of the ropinirole and 13% of the placebo-treated patients achieved the primary end-points, having a 20% or greater reduction in 'off' time and a decrease in the dose of levodopa between baseline and final visit.
Hobson, D., Pourcher, E., & Martin, W. [39]	prospective, randomized, double-blind, parallel-group trial	Ropinirole has been compared to placebo, levodopa, and bromocriptine in separate trials in early Parkinson's disease patients	a 12-week study involving 62 patients.The dose ranged from 0.5 mg to 5 mg bid.	ropinirole to be as effective as levodopa in mildly disabled patients
Miyasaki, J. M., et al. [43]	Experimental studies	To study the motor improvement between ropinirole versus levodopa	In the study (5 years), levodopa treatment resulted in a significantly greater increase in motor improvement than ropinirole treatment.Nearly 50% of patients develop motor complications and after 10 years nearly 100% of patients are affected by them.	For the course of the study, levodopa produced more motor improvement than ropinirole.
Brooks, D. J.[50]	A double-blind, randomised trial	Comparing ropinirole with levodopa plus benserazide	268 patients with early Parkinson's disease have been recently presented. Forty-seven per cent of ropinirole patients and 51% of levodopa patients completed the 5-year study; 34% of patients on ropinirole did so on monotherapy.	For patients on ropinirole who were given levodopa supplements, a lower dose of levodopa was required compared with patients on levodopa alone (427 mg/day v 753 mg/day respectively).
Rakshi, J. S., et al.[56]	Multinational study	To study the relative rates of progression of early Parkinson's disease (PD) in patients started on a dopamine agonist, ropinirole, or L-dopa.	45 patients with early PD [mean age 61 +- 9.8 SD and mean symptom duration, 26 +- 16 SD months]	A significantly lower prevalence of dyskinesias compared to L-dopa.
Deleu et al.[57]	A randomized, double-blind, placebo-controlled trial.	To compare the development of motor complications after pramipexole 0.5mg three times daily versus levodopa/ carbidopa monotherapy (100/25mg three times daily)	The efficacy of pramipexole in 335 de novo PD patients	Somnolence was more common in pramipexole-treated patients than in levodopa-treated patients (32 vs 17%).
Liebermann et al. [32]	A multicenter, double-blind and randomized study.	To compare the efficacy of patients treated with a placebo and ropinirole.	The study included 95 Hoehn & Yahr stages II to IV patients with motor fluctuations and off-phenomena.	Compared with placebo, ropinirole-treated patients needed 20% less levodopa and their off-time was reduced by 20%.
Perugi, Giulio, et al.[60]	A prospective, randomized double-blind study	To compare the safety of ropinirole and levodopa in the early stage of Parkinson's disease (mean age = 46 years).	Two groups were taken for the trial.	Ropinirole proved to be substantially superior to levodopa. The occurrence of dyskinesias was significantly higher in the levodopa group than among the ropinirole-treated patients (p = 0.001).

In the intention to treat the ropinirole arm of the study (including levodopa-rescued patients), the incidence of dyskinesia was still significantly reduced (20% for ropinirole *v* 46% for levodopa; p < 0.001). Adverse experiences, typical for dopaminergic agents caused 27% of ropinirole patients and 29% of levodopa patients to withdraw from the study prematurely (not significantly different).[50]

A 3-year, randomized, double-blind study comparing the actions of ropinirole and bromocriptine in 335 patients with early Parkinson's disease has also just been completed.[55] Patients initially received either ropinirole (n=168) or bromocriptine (n=167) as monotherapy. Where insufficient relief from symptoms was achieved, supplementary levodopa was added and was the study allowed to continue.[50]

A recent multinational study by Rakshi, J. S., et al. (Rascol, 2000), has shown ropinirole to be an effective symptomatic treatment in early PD for up to five years and its early use results in a significantly lower prevalence of dyskinesias compared to L-dopa.[56]

A large randomized, double-blind, placebo-controlled trial by Deleu et al. compared the development of motor complications after pramipexole 0.5 mg three times daily versus levodopa/carbidopa monotherapy (100/25 mg three times daily).[58] At 94 weeks, pramipexole monotherapy resulted in significantly less development of motor fluctuations (28 vs 51% in the levodopa group). Despite this, the mean improvement in total UPDRS score from baseline to 23.5 months was significantly greater in the levodopa group than in the pramipexole group (9.2 vs 4.5 points). Somnolence was more common in pramipexole-treated patients than in levodopa-treated patients (32 vs 17%).[57]

The approval of ropinirole was also based on its efficacy in patients who were initially treated with levodopa during their long-standing disease. ***Liebermann et al.***[32] performed a multicenter, double-blind and randomized study that included 95 patients in Hoehn & Yahr stages II to IV with motor fluctuations and off-phenomena. All of them took levodopa. 46 patients were treated with ropinirole and 46 with placebo. Duration of disease averaged 8.6 years in the ropinirole group vs. 9.4 years in the placebo group.[32]

The therapy with levodopa (plus carbidopa) has been carried out for on average 7.3 years in the ropinirole group and 7.5 years in the placebo-treated patients. The incidence of off phenomena was 39.3% in the ropinirole-treated and 43.4% in the placebo-treated groups. There were no differences in the age or gender of patients of the two groups.[32] Compared with placebo, ropinirole-treated patients needed 20% less levodopa and their off-time was reduced by 20%.[59,32]

In a prospective, randomized double-blind study — the so-called Study — that was run over five years, Rascol et al.[44] compared the safety of ropinirole and levodopa in the early stage of Parkinson's disease (mean age = 46 years).[60]

At the endpoint of the study — the onset of dyskinesias — ropinirole proved to be substantially superior to levodopa. The occurrence of dyskinesias was significantly higher in the levodopa group than among the ropinirole-treated patients (p = 0.001), with the difference between the two groups increasing throughout the trial. After five years, 20% of the ropinirole-treated patients developed dyskinesias compared to 45% of the levodopa-treated patients (p < 0.001). Before the addition of levodopa, dyskinesias were seen in 5% of ropinirole- and 36% of the levodopa-treated patients[59,44,60]

Although previously many physicians avoided levodopa for early Parkinson's disease treatment, recent research does not support this approach. One trial (PD MED)[62] found that individuals randomly assigned to begin treatment with levodopa (n = 528) had small but persistent mobility benefits 7 years later compared with individuals treated initially with dopamine agonists (n = 462) Or MAO-B inhibitors (n = 460).[61,62]

More than 40% of individuals treated with oral dopamine agonists (ropinirole, pramipexole) experience impulse control disorders (eg, gambling, compulsive spending, abnormal sexual and eating behaviours, compulsive medication use).[63] Individuals who discontinue the use of dopamine agonists, often due to impulse control disorders, experience withdrawal symptoms (eg, anxiety, panic attacks, irritability, diaphoresis, pain, and drug cravings) 15 to 20% of the time. Due to this, the dopamine agonist can sometimes not be discontinued despite serious adverse events such as impulse control disorders.[61,64,65]

In terms of symptomatic effects, levodopa proved to be better than dopamine agonists.

Levodopa's symptomatic effect also proved better than ropinirole,[44] pramipexole,[68] pergolide,[68,75,69] lisurid,[76] and cabergoline.[77] The results of these individual studies are confirmed by systematic reviews showing that levodopa monotherapy – in general – produced lower UPDRS scores than cabergoline, pramipexole, ropinirole,[70,83] and bromocriptine, lisuride, pergolide.[66,72]

Levodopa is more efficacious than any orally active dopamine agonist monotherapy. The proportion of patients able to remain on agonist monotherapy falls progressively over time to < 20% after 5 years of treatment (Class I: bromocriptine),[71,78,80] cabergoline,[79] pergolide,[81] pramipexole),[82] and ropinirole.[73,74, 87] For this reason, after a few years of treatment, most patients who start on an agonist will receive levodopa as a replacement or adjunct treatment to keep control of motor Parkinsonian signs.[66]

Rascol et al. (May 18 issue)1 summarize the results of their study by stating that Parkinson's disease is best managed with ropinirole alone as the initial treatment, with levodopa used as a supplemental, second step if necessary. This recommendation is based on their finding that the risk of dyskinesias (medication-induced chorea) is lower with ropinirole.[66]

Over 4 to 5 years, patients initially treated with a dopamine agonist were observed to experience lower motor complications, especially dyskinesia. The overall benefit was generally comparable across groups as assessed by the

quality of life (QOL) or Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living (ADL) scores. However, the reduction of motor disability, as assessed by UPDRS motor scores was greater in patients treated with levodopa alone. Because the incidence and severity of motor complications increase with disease duration,1,4 these observation periods may be too short to accurately assess the potential long-term benefit of initial treatment with a dopamine agonist compared with levodopa.[84]

We found that ropinirole 24-hour is effective in reducing "off " time compared to placebo in patients with PD not optimally controlled with levodopa. Patients receiving ropinirole 24-hour experienced a reduction in "off " time by an average of 2.1 hours (adjusted treatment difference of 1.7 hours), which was both significant and clinically relevant. These benefits for ropinirole 24-hour were observed from week 2 through week 24.[85]

The decrease in "off " time in the ropinirole 24- hour group was accompanied by an average increase in "on" time of 1.6 hours (treatment difference of 1.7 hours). At the study end (week 24), there was a significant treatment difference in favour of ropinirole 24- hours for "on" time without troublesome dyskinesia.[85]

The use of ropinirole can delay the use of L-dopa for up to several years Sethi et al., for example, employed ropinirole as monotherapy and achieved adequate efficacy in nearly half of the 116 patients treated for one year. In a 3-year study, Korczyn et al. found that 60 % of the patients treated with ropinirole did not require L-dopa.

In study 056, 34% of the patients were still receiving ropinirole as monotherapy after 5 years; in the extension study, even 13.9 % were receiving ropinirole as monotherapy after as long as 8.5 years.[86]

In a study by ***Anette Schrag***, dyskinesias were observed under L-dopa at a rate of 11.2 % within 17 months as compared to 1.2 % under ropinirole. Similar results were found in the REAL-PET study (Requip as Early therapy versus L-dopa -PET study;) where the rate of dyskinesias in the L-dopa group was 26.7 % and 3.4 % in the ropinirole group.[86]

Lieberman and colleagues reported that, in patients with advanced Parkinson's disease, ropinirole as an adjunct treatment to L-dopa reduced the dose of L-dopa and the time spent "off". In that study, there was a mandatory reduction in L-dopa dose, and the primary efficacy endpoint was the proportion of "responders"—patients who achieved a 20% reduction in L-dopa dose and a 20% reduction in time spent "off" between baseline and endpoint.[87]

A summary of preclinical and clinical studies is presented. Ropinirole is safe and efficacious as monotherapy in the treatment of early PD[1-7] and as an adjunct to levodopa in more advanced cases.[88]

The safety and efficacy of ropinirole and bromocriptine as an adjunct therapy in patients with Parkinson's disease (PD) not optimally controlled by L-dopa. In patients receiving a relatively high dose of L-dopa and requiring the addition of a dopamine agonist to control motor fluctuations or dyskinesias, ropinirole was significantly more effective than bromocriptine.[89]

A total of 423 patient records were randomly selected and reviewed by 52 neurologists and are the subject of the present study. Out of this total, 418 records were assessable (the records of 5 patients lacked adequate efficacy data) and included for analysis: 24% of these records corresponded to patients who received RPN in monotherapy and 76% received it as an adjuvant to levodopa treatment.[90]

Ropinirole is effective as mono- and combination therapy in PD. Previous studies have used a maximal dose of 24 mg/day; the present study assesses the effect of higher doses (up to 36 mg/day) on patients with motor fluctuations. Outcome measures were changes in the motor function score of the Unified Parkinson's Disease Rating Scale, the duration of dyskinesias and reductions in levodopa dose.[91]

In a randomized, double-blind, non-inferiority, crossover study, ropinirole prolonged-release was shown to have comparable efficacy and tolerability to immediate-release ropinirole in early PD patients, with significantly greater compliance. Patients on ropinirole prolonged-release were also more likely to require less daily levodopa. Ropinirole prolonged release is a safe and effective treatment option for both early and advanced PD.[57]

12-month treatment with ropinirole continued to provide effective symptomatic control in patients with early PD and was generally well tolerated. Ropinirole-treated patients continued to do well over the 6-month extension study without the initiation of levodopa therapy. Overall, the number of patients who completed the 12-month study and did not receive additional symptomatic therapy with levodopa was much greater for the ropinirole-treated group compared with the placebo-treated group. These results extend the findings of the initial 6-month study and support the use of ropinirole as an effective initial option for the treatment of patients with early PD.[57]

This study shows that the early use of the dopamine agonist ropinirole significantly reduces the risk of dyskinesia in patients with Parkinson's disease. When all the patients randomly assigned to ropinirole were compared with those randomly assigned to levodopa, the risk of dyskinesia was lower by a factor of almost three in the ropinirole group.[44]

Conclusion

Ropinirole has several potential advantages over levodopa. Agonists do not require metabolism to an active form (as is the case for levodopa) and do not compete with dietary amino acids for active transport across the gut epithelium and blood-brain barrier. Concluding the results of various studies the use of ropinirole is an effective option for the treatment of patients with early PD. The risk of dyskinesias is lower with ropinirole than with levodopa. Levodopa can be given with ropinirole to patients with advanced PD after some years to delay motor complications.

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