An update on the diagnosis and treatment of Parkinson disease

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Parkinson disease is the second most common neurodegenerative disorder after Alzheimer disease.[1] Parkinson disease typically develops between the ages of 55 and 65 years and occurs in 1%–2% of people over the age of 60 years, rising to 3.5% at age 85–89 years.[2–4] About 0.3% of the general population is affected, and the prevalence is higher among men than women, with a ratio of 1.5 to 1.0.[5] Parkinson disease may be more common among white people than those of Asian or African descent; however, the data are conflicting.[4,6] In 2011, the estimated number of people living with Parkinson disease in Canada had reached 85 200.[7] By 2031, the projected number of people with this disease will double.[1,7]

Management remains complicated over the course of the disease and should be individualized based on the patient's quality of life at each stage of disease. There have been many advancements in the management of Parkinson disease and ongoing research. Many options are now available. This review presents current treatment strategies and recommendations in managing motor and nonmotor symptoms in the various stages of Parkinson disease. Methods for developing this review are outlined in Box 1.

What is the pathophysiology of the disease?

Parkinson disease is a neurodegenerative syndrome involving multiple motor and nonmotor neural circuits.[8,9] It is characterized by two major pathologic processes: (a) premature selective loss of dopamine neurons; (b) the accumulation of Lewy bodies, composed of α-synuclein, which become misfolded and accumulate in multiple systems of patients with Parkinson disease. It is unclear which process occurs first. Based on pathologic studies,[10] there is a stepwise degeneration of neurons over many years, with each affected site corresponding to specific symptomatology in Parkinson disease (Table 1). When motor symptoms become evident, there is 30–70% cell loss evident in the substantia nigra on pathologic examination.[11] The mainstay of therapy aims to replace dopamine with dopaminergic medications and modulate the dysfunctional circuit. Cognitive dysfunction, mood disorders and impulse control disorders are related to deficits of dopamine outside the basal ganglia or in serotonergic and noradrenergic systems.[12,13] Autonomic dysfunction has

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Box 1: Methods

We used Canadian and American national guidelines to inform this review, in addition to published systematic reviews that were known to us. We identified additional articles through MEDLINE literature searches using the search terms "Parkinson disease" and "diagnosis," "treatment," "pathology," "epidemiology" or "prognosis" from 1980 to present. In addition, we reviewed conference abstracts and reference lists from seminal articles, and clinical trials currently underway (clinicaltrials.gov). Where possible, we selected the most recent articles and the articles with the most robust level of evidence (such as randomized controlled trials and meta-analyses). We reviewed more than 300 citations, of which 179 are included in this review (including those within the appendices).

KEY POINTS

- Parkinson disease is the second most common neurodegenerative disorder after Alzheimer disease; its cause is unknown.
- Parkinson disease remains a clinical diagnosis, based on motor symptoms and signs; nonmotor symptoms, such as constipation, anosmia, rapid eye movement sleep behaviour disorder and depression, may precede motor symptoms by years.
- Factors such as symptom severity, degree of functional impairment and patient preference should be taken into account when choosing treatment. Levodopa remains the gold-standard therapy for treatment of motor symptoms of Parkinson disease.
- Motor fluctuations and dyskinesia will develop in most patients five to ten years into the disease while taking levodopa; many adjunctive oral therapies are available to reduce motor fluctuations.
- Surgical therapies, including deep brain stimulation and levodopa–carbidopa intestinal gel, may be offered to patients who continue to have troublesome motor fluctuations and dyskinesia.

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been related to pathologies outside the brain, including the spinal cord and peripheral autonomic nervous system.[14]

Who gets Parkinson disease?

The exact cause of Parkinson disease is unknown, but it is assumed to be the result of a combination of environmental influences superimposed on genetic predisposition or susceptibility (Table 2).[14–16] There is increasing evidence that the genetic and environmental insults leading to Parkinson disease commonly lead to abnormal forms of a normal protein, α-synuclein, which seems to contribute to cell death.[16,23] The onset of Parkinson disease can be categorized as juvenile (age < 21 yr), early onset (21–50 yr) and late onset (generally > 60 yr).[24,25] The juvenile form is rare, is often familial (in as many as 50% of cases), is most frequently associated with a parkin gene mutation and has an atypical presentation.[25,26] Of patients with Parkinson disease, 10%–16% have an affected first- or second-degree relative; first-degree relatives may have double the risk of Parkinson disease compared with the general population.[26–29] In early- and late-onset Parkinson disease, the frequency of a positive family history is not statistically different.[24]

How is the diagnosis made?

Currently, diagnosis of Parkinson disease is based on clinical features from history and examination, and over time based on the response to dopamine agents and the development of motor fluctuations.[30] Motor manifestations of the disorder (Table 3) begin asymmetrically, and commonly include a resting tremor, a soft voice (hypophonia), masked facies (initially presenting as reduced blink rate), small handwriting (micrographia), stiffness (rigidity), slowness of movements (bradykinesia), shuffling steps and difficulties with balance. A classic symptom is resting tremor, usually affecting one upper limb, although 20% of patients do not have it;[31] 30% may first present with tremor in a lower extremity, and there may also be a lip, jaw or even tongue tremor at rest.[31,46] Head and voice tremors are uncommon, and one should consider essential tremor in the differential diagnosis in such cases.[31] Of all the major features, bradykinesia has the strongest correlation with the extent of dopamine deficiency.[47] Diagnosis has been formalized by the criteria of the UK Parkinson's Disease Society Brain Bank,[31] with diagnostic accuracy of up to 90% (Box 2).[48]

Parkinson disease also has a multitude of nonmotor symptoms; some may precede the diagnosis, and others may present early or late (Table 3) after the diagnosis, based on motor features, is made. The frequencies of early nonmotor symptoms that may precede the diagnosis of Parkinson disease, including constipation, disorders of rapid eye movement sleep behaviour, depression and olfactory impairment, are listed in Table 3. Red flags suggesting an alter-

Table 1: Braak staging of Lewy body deposition[10]

Stage	Sites affected by Lewy bodies	Major symptoms
I	Dorsal motor nucleus of the vagus nerve and olfactory tract	Constipation, anosmia
II	Locus coeruleus and subcoeruleus complex	Sleep and mood dysfunction
III	Substantia nigra	Motor symptoms of Parkinson disease
IV–VI	Cortical involvement	Dementia, psychosis

Table 2: Risk factors for Parkinson disease

Nonmodifiable risk factors[14–16]	Modifiable risk factors	
	Increased risk	Possible decreased risk

• Age (mean age 65 yr)
• Sex (M:F = 1.5:1.0)
• Genetics (10% of cases)
  • *LRRK2* mutation (most common)
  • Glucocerebrosidase gene mutation
  • Parkin mutation (juvenile onset)
	• Industrial exposure[17]
	• Heavy metals (i.e., manganese, lead, copper)[16,19]
	• Pesticides (i.e., rotenone, paraquat)[15,21]
	• Obstructive sleep apnea (maybe in women)[22]
		• Smoking (may be protective)[18]
		• Caffeine (may lower risk, relative risk 0.69; does not imply causality)[20]

Note: F = female, M = male.

native diagnosis to idiopathic Parkinson disease, such as another parkinsonian syndrome, are listed in Appendix 1.

How do early- and late-onset disease differ in presentation?

Patients with early-onset Parkinson disease are less likely to have gait disturbance as the presenting symptom, but have more pronounced rigidity and bradykinesia than those with late-onset disease.[49,50] In one study, presentation with resting tremor occurred in 41% of patients with early-onset disease and 63% of those with late-onset disease,[49] but further studies have not shown a consistent difference for tremor onset between early- and late-onset Parkinson disease.[24] Patients with early-onset disease have a slower disease progression, delayed onset of falls and longer survival.[24] Treatment differences in early and late onset are outlined below.

What tests or investigations are available to help with diagnosis?

Parkinson disease is a clinical diagnosis, and magnetic resonance imaging (MRI) may be used only to exclude other causes, as listed in Appendix 1. Advancements in neuroimaging studies, including transcranial Doppler ultrasonography,[51] positron emission tomography (PET), single-photon emission computed tomography (SPECT), morphometric MRI studies, tractography, functional MRI and perfusion imaging are being used to differentiate idiopathic Parkinson disease from other parkinsonian disorders.[52,53]

Radionuclide imaging modalities like PET and SPECT, using a dopamine transporter ligand, have become the best approach to assess dopamine metabolism and deficiency. Tracer uptake is reduced maximally in the posterior or dorsal striatum and is asymmetric in Parkinson disease.[52,53]

A subgroup of patients suspected of having new-onset Parkinson disease will have no evidence of dopaminergic deficit on dopamine transporter SPECT and fluorine-18 fluoro-L-dopa PET imaging scans.[54] In this group of patients, progression of disease, by imaging or clinical measures, is minimal, as is their likelihood of developing idiopathic Parkinson disease.[54] However, a few may eventually be diagnosed with Parkinson disease, based on clinical progression, imaging and genetic evidence and a positive response to levodopa.[55]

There are currently no biomarkers of proven clinical utility. Cerebrospinal fluid levels of α-synuclein may predict cognitive decline but do not correlate with motor progression.[56]

How is Parkinson disease treated?

Dopaminergic medications are the mainstay of symptomatic therapy for motor symptoms in Parkinson disease. The mechanisms of action, starting and target doses and adverse effects of medications are summarized in Appendix 2, available

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Table 3: Early and late motor and nonmotor features in patients with Parkinson disease

Early motor features[30,31]	Early nonmotor features (may precede the diagnosis)	Late features (usually develop 5–10 yr after disease onset)[31–34]	Late nonmotor features[31–34]
• Difficulty turning in bed • Frozen shoulder • Stiffness, numbness or pain in limb • Micrographia[35] • Difficulty with fine finger movements (bradykinesia) • Tremor of hand, jaw, foot • Decreased facial expression • Decreased arm swing, dragging a leg • Soft voice ("Do people ask you to repeat yourself over the phone?")	• Constipation (30%)[34] • REM sleep behaviour disorder* (50%, often preceding the diagnosis by median of 14 yr)[36–38] • Depression occurs with a prevalence of 35% in Parkinson disease, and 10%–15% will have depression at the time of diagnosis[39] • Olfaction impairment (most consistent nonmotor feature predicting Parkinson disease); up to 97% of patients[34,40,41]	• Motor fluctuations • Dyskinesia (complication of dopaminergic treatment, more so with levodopa); typically choreiform, involving the neck, head, limbs and trunk • Gait freezing • Falls	• Dysphagia (50% at 15 yr)[42] • Neuropsychiatric symptoms (50% at 15 yr),[42] including hallucinations, sleep disturbance and dementia • Autonomic disturbances (70%–80%),[43,44] including sweating, orthostasis, sialorrhea and urinary dysfunction • Seborrheic dermatitis (usually involving the forehead, with flaky oily skin)

Note: HR = hazard ratio, REM = rapid eye movement.
*The risk of synucleinopathy (i.e., Parkinson disease, multiple system atrophy, Lewy body dementia) in patients with REM sleep behaviour disorder was reported to be 30% at 3 years, rising to 66% at 7.5 years.[45] Advanced age (HR 1.07), olfactory loss (HR 2.8), abnormal colour vision (HR 3.1), subtle motor dysfunction (HR 3.9) and nonuse of antidepressants (HR 3.5) identified higher risk of disease conversion.[45]

at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.151179/-/DC1. Discovered in the 1960s, levodopa was the first symptomatic treatment for Parkinson disease, followed by the availability of dopamine agonists and monoamine oxidase B inhibitors. Until recently, the decision regarding which treatment to initiate has been debated. There is no one medication that is recommended for treatment initiation currently, but factors such as symptom severity, embarrassment, ability to perform activities, cost and patient preference should be taken into account. If symptoms are very mild, the patient may choose not to begin therapy.[34,57]

Because patients with early-onset disease are more likely to develop levodopa-induced abnormal movements (dyskinesia), dopamine agonists are often introduced as initial treatment; however, this early advantage of dopamine agonists over levodopa diminishes over time (about 10 yr).[34] There is also some controversial evidence for neuroprotection with the monoamine oxidase B inhibitor rasagiline at the 1 mg daily dose;[58] however, its cost is not covered in most provinces and may require application to the exceptional access program, as is done in Ontario.

Because of the increased risk of neuropsychiatric adverse effects from dopamine agonists in late-onset Parkinson disease, levodopa is often started first.[34] Levodopa achieves somewhat better control of motor symptoms of Parkinson disease than dopamine agonists and monoamine oxidase B inhibitors, but dyskinesias and motor fluctuations develop after long-term use or high-dose treatment.[59] The patient will likely need multiple medication adjustments over time with the addition of adjunctive treatments.[60,61] Most patients taking dopamine agonists will also need levodopa after two to five years.[62] Nonmotor symptoms and their management are reviewed in Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.151179/-/DC1.

Because Parkinson-plus syndromes (e.g., multiple system atrophy and progressive supranuclear palsy), respond in the very early stages to levodopa, this medication should be tried for at least several months with doses up to 1000 mg/d before concluding nonresponsiveness.[63] The diagnosis should also be re-evaluated after a trial of levodopa. Responsiveness to levodopa occurs in about 80% of patients with idiopathic Parkinson disease.[63] Although bradykinesia and rigidity respond well to levodopa, this consistent response is not seen for tremor.[64]

Anticholinergics, such as trihexyphenidyl, may be used in patients with early-onset Parkinson disease and severe tremor, but not as a first choice owing to limited efficacy and propensity for neuropsychiatric adverse effects.[57] Recent data show that injections of botulinum toxin may effectively treat tremor from Parkinson disease.[65]

Behavioural addictions and impulse control disorders occur in 5% of patients with Parkinson disease and up to 20% of those taking dopamine agonists.[66,67] Risk factors for impulse control disorders include younger age (perhaps related to prescribing behaviour of dopamine agonists in this group), novelty-seeking personality, family history of addiction, use of dopamine agonists and prior history of impulse control disorders.[66]

Dopamine dysregulation syndrome is a form of addictive behaviour that occurs in up to 4% of patients and is characterized by compulsive overuse of dopaminergic medications, which are typically short-acting (e.g., levodopa and apomorphine), impairing physical, social and occupational functioning.[67] Punding involves repetitive, often purposeless, stereotyped behaviours, such as sorting or disassembling, and occurs in up to 15% of patients with Parkinson disease.[68] Impulse control disorders can occur anytime after starting dopamine agonists; dopamine dysregulation syndrome and punding can occur with use of short-acting dopaminergic agents, including levodopa.[34]

Antiparkinsonian medications should not be withdrawn abruptly to avoid acute akinesia or neuroleptic malignant syndrome. Dopamine agonists should not be rapidly discontinued because of the risk of dopamine agonist withdrawal syndrome (occurs in 15% of patients taking dopamine agonists; the risk is higher among those with impulse control disorders).[69–71]

About 40% of patients with Parkinson disease use one or more forms of alternative therapies to complement their standard treatments.[72] Exercise

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Box 2: Criteria of the UK Parkinson's Disease Society Brain Bank for diagnosing Parkinson disease[31]

- Bradykinesia and at least one of the following:
  - Rigidity
  - Resting tremor (4–6 Hz)
  - Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
- Exclusion of other causes of parkinsonism (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.151179/-/DC1)
- At least three of the following supportive (prospective) features:
  - Unilateral onset
  - Persistent asymmetry primarily affecting the side of onset
  - Resting tremor (hand, leg or jaw; low frequency [4–5 Hz], asymmetric, disappears with action)
  - Excellent response to levodopa (70%–100%)
  - Progressive disorder
  - Severe levodopa-induced chorea (dyskinesias)
  - Levodopa response for five years or more
  - Clinical course of 10 years or more

therapy may be considered as a means of improving motor function in patients with Parkinson disease, but there is no good evidence that it is neuroprotective.[73–75] There is good evidence for physiotherapy, but the effect often dissipates when the intervention stops.[75,76] Physiotherapy should address specific motor features such as falls, freezing and deconditioning. For patients with early disease, it is reasonable to encourage exercise (e.g., gym settings, regular walks or even dance therapy).[75,77] Speech therapy may be considered to improve speech volume, with evidence in favour of the Lee Silverman Voice Treatment.[78] Occupational therapy should be employed for practical home issues and activities of daily living,[75] and may be helpful with driving assessments.

Drugs that should be avoided

Drugs that block dopamine receptors can result in parkinsonism or substantially worsen motor symptoms in patients with Parkinson disease and may lead to neuroleptic malignant syndrome. These include neuroleptics, such as haloperidol, thioridazine, chlorpromazine, promethazine, fluphenazine, risperidone and olanzapine; antiemetics, such as prochlorperazine and metoclopramide; tetrabenazine; and antihypertensives, such as methyldopa.[79,80] Meperidine should be avoided in those receiving monoamine oxidase B inhibitors.[81]

Managing motor and nonmotor symptoms in advanced disease

Most patients respond well to levodopa; however, in 40%–50% of patients, motor fluctuations and dyskinesias will develop within five years of chronic levodopa treatment and in 70%–80%, after 10 years of treatment.[34,82,83] Motor fluctuations are unexpected variations in the motor response, which may be erratic, to dopaminergic therapy, whereas dyskinesias are unwanted and intrusive, predominantly choreiform, movements resulting from levodopa (Appendices 4 and 5, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.151179/-/DC1).[84] Dyskinesias are less likely to develop in patients receiving less than 400–500 mg per day of levodopa.[85] A higher cumulative incidence of dyskinesias, wearing off and on–off fluctuations in symptoms occurs in patients with early-onset disease and perhaps in women (Appendices 4 and 5).[24,61,82,86,87] Dyskinesias may indicate better response to medication, and most patients prefer to be "on" with dyskinesia than "off."[87]

In one study, 20% of patients with Parkinson disease had troublesome motor fluctuations and 4% had dyskinesias by five years, which were severe enough to require treatment change.[88] Catechol O-methyltransferase (COMT) inhibitors, such as entacapone, given with each tablet of levodopa–carbidopa; monoamine oxidase B inhibitors, such as rasagiline or selegiline; and dopamine agonists, such as pramipexole, ropinirole, rotigotine patch and bromocriptine, may be offered to reduce "off" time.[57] Ergot derivatives, such as bromocriptine, should be used with caution due to risks of pulmonary and cardiac valve fibrosis. Modified-release levodopa preparations, such as controlled-release preparations, may be used to reduce motor fluctuations, but should not be used as a first choice. There is evidence that use of combination forms of levodopa–carbidopa with COMT inhibitors is associated with earlier onset and increased frequency of dyskinesias.[89] Amantadine, an antiviral with antiglutamatergic effects, may be considered to reduce dyskinesias; it is effective in 60%–70% of patients (level C evidence, as defined in Appendix 2).[90] Axial symptoms, including postural instability and gait, tend to occur later in the disease and may be less responsive to dopaminergic therapies. There is evidence for trying cholinesterase inhibitors and/or methylphenidate (level U [Appendix 2]).[91]

In advanced Parkinson disease, many disabling nonmotor symptoms emerge that are not improved by levodopa.[42] Nonmotor symptoms and their management are reviewed in Appendix 3.

Available of disease-modifying therapies

No treatment has yet been found to be conclusively neuroprotective. Trials that have failed to show any convincing evidence of disease modification or slowed progression of Parkinson disease are listed in Appendix 6, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.151179/-/DC1.

What has changed in the treatment of advanced Parkinson disease?

In advanced Parkinson disease, the efficacy of levodopa can decline and fluctuate throughout the day switching between "on" and "off" medication periods.[92] The motor and nonmotor fluctuations mirror those seen in levodopa plasma concentrations resulting from levodopa's short half-life.[93] Providing continuous dopaminergic stimulation is the goal of treating fluctuations in patients with advanced Parkinson disease.[94–96] We now have surgical options, including deep brain stimulation and levodopa–carbidopa intestinal gel, to provide treatment to such patients. Currently, deep brain stimulation has the highest level of evidence with the largest

number of randomized controlled trials.[97] Emerging therapies currently being studied in Parkinson disease are listed in Appendix 7, available at www.cmaj.ca/lookup/suppl/doi :10.1503/cmaj.151179/-/DC1.

Deep brain stimulation

Deep brain stimulation was approved in 2002 as an adjunctive therapy in reducing motor fluctuation in advanced Parkinson disease (level C [Appendix 2]).[57] The globus pallidus interna and the subthalamic nucleus are accepted targets for this procedure, with similar improvements in motor function and similar adverse events.[98,99] Patients with subthalamic nucleus stimulation required lower doses of dopaminergic medications, but depression worsened after subthalamic nucleus stimulation and improved after globus pallidus interna stimulation. Most centres select patients for deep brain stimulation on the basis of the nature of the patient's symptoms and the likelihood of a response to the therapy (Box 3).

The response to deep brain stimulation is equal to the best response on levodopa, but more effective than medical therapy in improving "on" time without troublesome dyskinesias.[101,102] Deep brain stimulation typically improves levodopa-responsive symptoms (e.g., tremor, bradykinesia, rigidity) and on–off fluctuations and dyskinesias, whereas impairments in gait, balance and speech are less likely to improve. Patients should be considered for deep brain stimulation only if adequate trials of multiple medications for Parkinson disease (e.g., levodopa–carbidopa, dopamine agonists, monoamine oxidase B inhibitors and amantadine) have been unsuccessful.[100] Although duration of efficacy is not clearly established, patients who undergo deep brain stimulation may have sustained benefit for at least 10 years.[100] A recent study suggests that deep brain stimulation for Parkinson disease may be offered earlier for patients (mean age 52 yr, disease duration 7.5 yr) just beginning to have motor fluctuations.[103] Thalamic deep brain stimulation may be considered as an option in patients who predominantly have disabling tremor where subthalamic nucleus stimulation cannot be performed.[57]

Adverse events are typically related to lead placement during surgery for deep brain stimulation, and the most worrisome include infection, requiring device removal and antibiotics (1.2%–15.2%), and intracranial hemorrhage (5%), causing permanent deficit or death in 1.1% of patients.[100] Diathermy, electrocautery and MRI should be avoided in patients with deep brain stimulation.[104]

Surgery for deep brain stimulation can cost between US$35 000–$50 000 and $70 000–$100 000 for bilateral procedures.[105] The cost for this procedure is covered in Canada.

Levodopa–carbidopa intestinal gel

For patients who are not candidates for or decline deep brain stimulation, levodopa–carbidopa intestinal gel may be considered. This gel is pumped into the jejunum, via percutaneous tube insertion, recently approved for the treatment of motor fluctuations in Parkinson disease.[106,107] The dose of required levodopa–carbidopa intestinal gel is equivalent to the daily oral levodopa dose, but delivered continuously during the waking day (i.e., 16 hours), without concerns of reduced absorption. Unlike deep brain stimulation, there is no age limitation or neurocognitive exclusion to levodopa–carbidopa intes-

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Box 3: Candidacy for deep brain stimulation[100]

Good candidates

- Adequate response to dopaminergic therapy
- Presence of on–off fluctuations
- Age < 70 yr[84]
- Dyskinesia impairing quality of life
- Medication-resistant tremor
- Reasonable cognitive function

Borderline candidates*

- Severe dyskinesia with a poor on–off dopaminergic response
- On–off fluctuations with moderate cognitive function
- On–off fluctuations with a poor on–off dopaminergic response
- Medication-resistant tremor with moderate cognitive dysfunction
- Medication-resistant tremor with a poor on–off dopaminergic response

Poor candidates

- Severe dementia
- Severe autonomic dysfunction
- Poor dopaminergic response
- Atypical parkinsonism (e.g., corticobasal degeneration, progressive supranuclear palsy, multiple system atrophy and Lewy body dementia)
- Unstable psychiatric disease
- Absence of a dedicated caregiver

*The risks and benefits of deep brain stimulation must be carefully weighed by a multidisciplinary team.

Table 4: Prognostic factors in Parkinson disease[57]

Predictors of a more benign course	Predictors of a more rapid course
• Early onset[24]	• Late onset[24]
• Tremor-predominant	• Male sex[118]
• Female sex[118]	• Postural instability (predominant gait difficulty)
	• Rigidity or bradykinesia as first symptom
	• Dementia
	• Poor response to levodopa
	• Associated comorbidities (e.g., stroke)

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tinal gel.[84] However, patients with severe dementia who may be unable to retain a jejunal tube are generally excluded.

Administration of levodopa–carbidopa intestinal gel has been shown to result in faster absorption, comparable bioavailability and reduced intrasubject variability in levodopa concentrations compared with oral levodopa–carbidopa.[108] Studies of levodopa–carbidopa intestinal gel in advanced Parkinson disease have shown a significant reduction in motor fluctuations and dyskinesias, but do not eliminate them completely.[84,109,110] In a seven-year follow-up study involving 59 patients with advanced Parkinson disease treated with levodopa–carbidopa intestinal gel, 90% of patients reported improvement in quality of life, autonomy and clinical global status.[111]

Discontinuation has been reported in 19%–25% of patients receiving levodopa–carbidopa intestinal gel who were followed for two to seven years; discontinuation was owing to adverse drug reactions, procedure- and device-related events, poor compliance and/or lack of efficacy.[111,112]

The cost of the gel is about Can$166 per day or roughly $60 000 per year,[113] and may require provincial approval applications for coverage.

What is the prognosis?

Life expectancy is decreased in Parkinson disease (odds ratio 2.56, i.e., the mortality risk is 2.56 times higher than similar age-matched people without Parkinson disease), and medical treatments do not appear to alter mortality or delay the onset of nonmotor symptoms.[114] Although progression is slower in patients with early-onset disease and there is longer absolute survival, this comes at the expense of increased years of life lost (11 yr lost in early-onset disease v. 4 yr in late-onset disease).[24,115] Late-onset Parkinson disease is associated with more rapid disease progression and cognitive decline,[116] which may be related to a lack of compensatory strategies against cell death.[24] Data on the long-term outcomes and in the older population are lacking.[117]

Prognostic factors are summarized in Table 4. Patients with early-onset disease were slower to reach stage III–V on the Hoehn and Yahr scale[119] (Appendix 8a, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.151179/-/DC1). The distribution of Hoehn and Yahr staging according to disease duration is listed in Appendix 8b. In the Rotterdam Study, Parkinson disease was associated with an increased risk of dementia (hazard ratio [HR] 2.8) and increased risk of death (HR 1.8). When dementia prevalence was controlled for, risk of mortality was only slightly higher than among the general population.[120]

Conclusion

Parkinson disease is a neurodegenerative disorder that is clinically diagnosed based on its motor features, with nonmotor symptoms being recognized commonly. The etiology remains unknown, but includes a combination of genetic and environmental risk factors, most commonly age and sex. Factors associated with increased mortality may include severity of parkinsonism, rate of worsening of parkinsonism, poor response to levodopa, early gait dysfunction and symmetry of parkinsonism. Some of these features may account for the possibility of a misdiagnosis of a Parkinson-plus syndrome as idiopathic Parkinson disease, and it is important to recognize this challenge in the differential diagnosis.

Although no neuroprotective treatments are yet available, many medical and surgical therapies exist that may be used in different stages throughout the course of disease for symptomatic treatment of both motor and nonmotor features. With the variety of ongoing trials on emerging therapies, we may see better options in the near future.

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