Parkinson's disease guidelines for pharmacists

Tejal Patel, BScPhm, PharmD; Feng Chang, BScPhm, PharmD; on behalf of Parkinson Society Canada

Introduction

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder, characterized by the loss of dopaminergic neurons from the substantia nigra that subsequently results in the loss of control of voluntary movement over time.¹⁻³ An estimated 100,000 Canadians have PD, and the incidence rate is between 10 to 20 per 100,000.⁴ Although younger people are diagnosed with PD, it is often thought of as a disease of the elderly, and indeed, the mean age of onset is 60 years, with 85% of individuals diagnosed with PD being older than 65 years.^{1,2,4} Over the course of 6 years, between 1993 and 1999, the prevalence of PD increased by 26% in Ontario, related in part to the increase in the population of those aged 65 years and over.⁵ A review by Health Canada in 1998 indicated that PD is associated with substantial direct (\$87.8 million) and indirect (\$470.3 million) costs.⁴ Although 70% of the cost is associated with long-term disability, life expectancy is also significantly shorter, with premature mortality accounting for 14.1% of the cost of the disease.^{2,4}

Although the clinical presentation can vary from one individual to another, patients will typically present with complaints of asymmetrical (i.e., more on one side of the body than the other) tremors at rest in one extremity, whether it be the arm or the leg, and stiffness or rigidity and/or slowness in movement (bradykinesia). Over time, individuals will develop a shuffling gait and postural instability (see Table 1 for a complete list of the motor features of PD).^{1,2} Motor symptoms are thought to result when 60% to 70% of dopaminergic neurons have been lost.² The loss of dopaminergic neurons results in a deficiency of dopamine, the primary neurotransmitter

involved in the coordination of movement. Currently, the pharmacotherapy of PD is primarily related to replacing dopamine or mimicking the activity of dopamine. As the disease progresses, patients struggle to maintain the balance between the positive and negative effects of pharmacotherapy, often requiring multiple adjustments of drug doses and dosing regimens as well as the addition and removal of adjuvant drugs.^{1,3}

Community pharmacists are highly visible, easily accessible health care providers who are valued by patients for their knowledge about medications.⁶ Pharmacists are well trained to address medication-related concerns and are the ideal health professionals to assess and refer patients requesting assistance with determining the treatment for symptoms indicative of PD. Additionally, pharmacists have long-standing established relationships with their patients and comprehensive appreciation of their patients' drug therapy, whether prescribed by the patient's family physicians or specialists or obtained by the patient for self-care. Pharmacists can therefore support both patients and physicians in the choice, adjustment and monitoring of ongoing pharmacotherapy for safety, effectiveness, drug interactions, affordability and adherence.

Canadian Guidelines on PD

The Canadian Guidelines on PD (CGPD) were developed to address the need to provide health care providers who treat individuals with PD with a tool to guide the best management of the disease.⁷ The CGPD are the result of a joint effort by specialists in the treatment of movement disorders, family physicians, allied health professionals, individuals diagnosed with PD and patient advocacy groups such as Parkinson Society

TABLE 1 Clinical presentation of motor features of PD

Symptom	Description
Tremors	Asymmetrical presentation of pill-rolling, 4- to 6-Hz resting tremors initially, which may progress to bilateral tremors at rest in all extremities.
Rigidity	Cogwheel or lead-pipe rigidity on clinical examination of joints.
Akinesia or bradykinesia	Patients may complain of slowness in movement, loss of dexterity, smaller handwriting (micrographia). People with PD may appear to have a decreased facial expression (masked facies) and/or decreased blinking rate. Speech may become softer (hypophonic). Patients may present with a reduced arm swing.
Postural instability	Patients may have gait disturbance and may shuffle and have a stooped posture. Patients may complain of a transient inability to walk (freezing), although this occurs with more advanced disease.

PD, Parkinson's disease.

Canada.⁷ The aim of the CGPD is to improve the care for all Canadians who have been diagnosed with PD through the application of

- best published evidence,
- expert consensus where there is a lack of evidence,
- practical clinical advice,
- patient involvement in the choice of treatment and informed decision-making, and
- relevance to the Canadian health care system.

A comprehensive description of the guideline development process is provided with the publication of the CGPD in the *Canadian Journal of Neurological Sciences*.⁷ Since there are other current, high-quality guidelines available for the management of PD, the goal of the CGPD was to review these guidelines to select the recommendations most relevant to the Canadian health care provider.

The CGPD are organized into 4 sections, each addressing one important aspect of the care of a patient with PD: communication, diagnosis and progression, treatment of motor symptoms and features, and treatment of nonmotor symptoms. Issues related to mental health, sleep disorders and autonomic dysfunction are illuminated further in subsections under the section addressing the features and treatment of nonmotor symptoms of PD.

In an effort to increase awareness and enhance the contribution by pharmacists in the care of the individual with PD, we present those

recommendations that we believe are most relevant to pharmacists, summarized in 4 sections: communication; diagnosis; prognosis, neuroprotection, and treatment; and treatment of nonmotor features of PD. Each of these sections cites the original recommendations in the CGPD for easy reference. The complete recommendations, discussion and review of the background are available at www.parkinsonclinicalguidelines.ca.

I. Communication

Good communication is the key to assisting patients, whether it is answering queries about the disease process, medications used to treat it, or helping patients navigate the health care system. Communication should be designed to meet the needs of the patient with PD.

Recommendations. Pharmacists should do the following:

- Empower people with PD to participate in the judgment and choices about their own care.
- Tailor information to the needs of the individual.
- Provide both verbal and written material.
- Frequently reinforce information, especially with those people with PD who are cognitively impaired and/or are depressed.
- Inform family and caregivers about the condition, entitlement to care assessments and support services available.

(CGPD recommendations: C1-C5).

II. Diagnosis

As outlined earlier, the clinical presentation of PD is characterized by tremors, rigidity, bradykinesia and postural instability. Patient complaints or visual observation of any of these symptoms should result in advising patients to seek an assessment and diagnosis from a family physician or specialist immediately (see Figure 1 for summary of identification, diagnosis and prognosis in PD).

Recommendations. Pharmacists should do the following:

- Suspect PD in people presenting with or complaining about tremors, stiffness, slowness, balance problems and/or gait disorders.
- Refer such patients to their family physician immediately for an assessment, diagnosis and further referral to a specialist.

(C9, C11).

III. Prognosis, neuroprotection, and treatment

Prognosis

The rate of progression of PD is dependent on a number of factors such as age, presence of comorbidities and primary symptom of presentation.

Recommendations. Pharmacists should expect a more rapid rate of motor progression in newly diagnosed PD if, at onset, the person is/does the following:

- Is male or older.
- Presents with rigidity/hypokinesia as an initial symptom. Such persons may also develop cognitive decline and dementia earlier.
- Presents with associated comorbidities such as stroke, auditory deficits, visual impairments and/or postural instability/gait difficulty.

Pharmacists can expect a slower rate of progression in newly diagnosed PD in persons

- who present with tremors as the primary symptom. Such persons may also experience benefit from levodopa for a longer period of time.

(C16-C19).

Neuroprotection

Neuroprotection in PD has been defined as an intervention with the potential to slow, stop or reverse the progression of PD.⁸ Although none of the medications used in the treatment of PD has been conclusively shown to have this effect, clinical trials with other agents are ongoing.

Recommendations. Pharmacists should do the following:

- Not recommend vitamin E, coenzyme Q10, dopamine agonists or monoamine oxidase inhibitors for neuroprotection in PD, except in the context of clinical trials.
- Understand that there is no long-term evidence to recommend levodopa for neuroprotection.

(C21-C24).

Treatment

The treatment for PD is primarily pharmacological, although an increasing number of non-pharmacological treatments are gaining favour. Surgical treatment for PD is presently limited to patients who have advanced disease and in whom pharmacological treatment is failing to manage motor symptoms. Only a few highly specialized centres offer these treatment options, thereby limiting access.

With the progression of PD, a patient's medication may need to be finely adjusted, as it often becomes difficult to balance side effects with the therapeutic effects of the medication (see Table 2 for side effects of medications used in the treatment of PD). Patients will develop motor complications such as "wearing off" (where the duration of the beneficial effect of levodopa becomes progressively shorter), "on/off" (where beneficial effects of the treatment are unpredictable), "freezing" (where there is no beneficial effect of levodopa for periods of time), and dyskinesias (involuntary movements). During this time, pharmacists can serve as invaluable partners in the care of people with PD by assisting with complex medication schedules, addressing side effects, assisting with different formulations of medications, obtaining approval for medications on emergency release, ensuring appropriate intake to maximize the absorption of medications and guiding the choice of medication based on patient preference, other concurrent medications and medical conditions, and affordability.

Recommendations. Prior to commencing initial drug treatment for early PD, pharmacists should do the following:

- Ensure that the drug choice is based on the clinical and lifestyle characteristics of the patient and patient preference.
- Ensure that the patient is aware of the short- and long-term benefits and drawbacks of the drug classes.
- Be aware that levodopa, dopamine agonists and monoamine oxidase inhibitors may be used to initiate symptomatic treatment.
- Be aware that amantadine may be used as a treatment in early PD but is not a drug of first choice.
- Be aware that anticholinergics may be used as a treatment in young patients with early PD and severe tremors but are not drugs of first choice, given the limited efficacy and propensity to cause neuropsychiatric side effects.
- Be aware the β -adrenergic agonists may be used to treat postural tremors in selected people with PD but are not drugs of choice.
- Be aware that nonergot dopamine agonists are preferred over ergot-derived dopamine agonists for the treatment of PD.
- Ensure that the baseline erythrocyte sedimentation rate, renal function result, and chest radiograph finding have been obtained for those patients prescribed an ergot-derived dopamine agonist.

(C29, C30, C33, C35-C41).

During pharmacotherapy for PD, pharmacists should do the following:

- Assist with the clinical monitoring of safety and effectiveness.
- Assist with medication adjustment.
- Ensure that antiparkinsonian medications are administered at appropriate times.
- Ensure that antiparkinsonian medications are adjusted after a discussion with a specialist.
- Ensure that antiparkinsonian medications are not withdrawn abruptly or allowed to fail suddenly due to poor absorption (e.g., gastroenteritis, abdominal surgery) to avoid the potential risk for akinesia or neuroleptic malignant syndrome.

- Ensure that patients are not withdrawn from their antiparkinsonian drugs (so-called drug holidays) because of the risk of neuroleptic malignant syndrome.
- Assist patients with keeping the dose of levodopa as low as possible to maintain good function in order to reduce the development of motor complications.
- Not recommend modified-release levodopa preparations to delay the onset of motor complications in people with early PD.
- Titrate dopamine agonists to clinically effective doses. If side effects prevent this, recommend replacing this drug with another dopamine agonist or a drug from another class.
- Be aware of dopamine dysregulation syndrome (impulse control disorders), an uncommon disorder in which dopaminergic medication misuse is associated with abnormal behaviours, including hypersexuality, pathological gambling, and stereotypical motor acts.

(C25-C28, C31, C32, C34, C53).

In patients who present with motor fluctuations, pharmacists should do the following:

- Recommend entacapone and/or rasagiline to reduce off time.
- Recommend pramipexole or ropinirole to reduce off time.
- Recommend modified-release levodopa preparations to reduce motor fluctuations but not as drugs of first choice.
- Recommend amantadine to reduce dyskinesias.

(C42-C45).

IV. Nonmotor features of PD

Nonmotor features of PD have been recognized as occurring in persons with PD, worsening disability and significantly impacting quality of life. The frequently occurring nonmotor features of PD are highlighted in this section, followed by recommendations for the treatment of these conditions.

Depression

Recommendations. In the management of patients with PD and depression, pharmacists should do the following:

FIGURE 1 Summary of the identification, diagnosis and prognosis in Parkinson's disease

- Personalize the approach to management, taking into consideration patients' coexisting therapy.
- Recommend amitriptyline as an option for drug therapy.

(C60, C61).

Psychosis

Recommendations. In the management of patients with PD and psychosis, pharmacists should do the following:

- Refer patients for medical evaluation and treatment for precipitating conditions.

- Reduce polypharmacy, reduce or stop anticholinergic antidepressants, and reduce or stop anxiolytics and/or sedatives.
- Recommend gradually withdrawing any antiparkinsonian medications that might have triggered psychosis: anticholinergics, amantadine, dopamine agonists, monoamine oxidase B and catechol-O-methyl transferase inhibitors, and levodopa. Note: Stopping antiparkinsonian drugs can worsen motor symptoms.
- Recommend no treatment for mild psychotic symptoms if they are well tolerated by the patient and caregiver.

TABLE 2 Medications for PD⁹

Drug (trade name)	Dosage	Adverse effects	Comments
Anticholinergic drugs: block cholinergic activity in the brain.			
Benztropine (Cogentin)	Initial: 0.5 mg daily Usual: 1-2 mg/d Maximum: 6 mg/d administered 1-4 times daily Titration: adjust dose in 0.5-mg increments every 5-6 days	Anhidrosis, nausea/vomiting, constipation, confusion, memory impairment, depression, hallucinations, weakness, tachycardia, blurred vision	May help with drooling; use caution in the elderly as they can cause confusion and cognitive impairment
Trihexyphenidyl (Artane)	Initial: 1 mg daily Usual: 6-10 mg/d administered 3-4 times daily Maximum: 6-10 mg/d Titration: increase 2 mg every 3-5 days		
COMT inhibitors: reversibly and selectively inhibit COMT.			
Entacapone (Comtan)	Initial: 200 mg with each dose of levodopa/carbidopa Maximum: 8 times daily (1600 mg/d)	Nausea, dyskinesias, orthostatic hypotension, syncope, dizziness, fatigue, hallucinations, somnolence, diarrhea, constipation, vomiting, brown-orange urine discoloration	Adjunctive treatment with levodopa; liver function test every 6 months
Dopamine agonists (nonergot derived): dopamine agonist binding to the D ₂ subfamily of dopamine receptors; also shown to bind to D ₃ and D ₄ receptors and believed to stimulate dopamine activity in the striatum and substantia nigra.			
Pramipexole (Mirapex)	Immediate release: Initial: 0.125 mg 1-3 times daily Usual: 0.5-1.5 mg 3 times daily Maximum: 4.5 mg/d Extended release: Initial: 0.375 mg daily Maximum: 4.5 mg/d Titration: gradually increase every 5-7 days	Symptomatic hypotension, somnolence, dyskinesias, weakness, nausea/vomiting, constipation, hallucinations, impulse control, rhabdomyolysis, pleural/retroperitoneal fibrosis	Dosing adjustment needed in renal impairment
Ropinirole (Requip)	Immediate release: Initial: 0.25 mg 3 times daily Usual: 1-8 mg 3 times daily Maximum: 24 mg/d Extended release: Initial: 2 mg daily for 1-2 weeks Maximum: 24 mg/d Titration: gradually increase every 5-7 days		

TABLE 2 (continued)

Drug (trade name)	Dosage	Adverse effects	Comments
Dopamine agonists (ergot derived)			
Bromocriptine (Parlodel)	Initial: 1.25 mg 3 times daily Usual: 10-30 mg/d Maximum: 100 mg/d Titration: gradually increase by 2.5 mg/d every 1-2 weeks	Impulse control disorders, sedation, pleural/ retroperitoneal fibrosis, dizziness, fatigue, headache, constipation, nausea, weakness, rhinitis, hypotension, Raynaud's phenomenon, hypoglycemia, increased risk of infection	Monitor for cardiac valvular fibrosis
Cabergoline (Dostinex)	Initial: 0.25 mg daily Maximum: 2-6 mg/d Titration: increase 0.5-1 mg every 1-2 weeks		
Dopamine precursors:			
Levodopa: dopamine precursor; crosses the blood-brain barrier and is converted to dopamine.			
Benserazide and carbidopa: inhibit the peripheral plasma breakdown of levodopa.			
Levodopa/benserazide (Prolopa) Carbidopa/levodopa (Sinemet)	Initial: 100/25 mg 1-3 times daily Usual and maximum dose: patient dependent Titration: increase by 100/25 mg every 3-4 days	Nausea/vomiting, confusion, orthostatic hypotension, hallucinations, hypersexuality, somnolence, gambling behaviour, melanoma	Long-term treatment associated with motor fluctuations and dyskinesias
Carbidopa/levodopa (Duodopa intestinal gel)	Initial: 1:1 ratio to/from oral tablet formulations Morning bolus dose: usually 100-200 mg levodopa (5-10 mL) Maximum: 300 mg levodopa (15 mL) Continuous maintenance dose: usually 40-120 mg levodopa per hour (2-6 mL/h) for up to 16 hours; adjust in increments of 2 mg/h (0.1 mL/h); range: 20-200 mg levodopa per hour (1-10 mL/h)		For intestinal gel therapy, any condition that prevents the placement of a percutaneous endoscopic gastrostomy tube
Carbidopa/levodopa controlled release (Sinemet CR)	Initial: 50 mg carbidopa/200 mg levodopa daily Titration: may adjust dosage every 3 days		Useful at dopamine ≥300 mg/d; slower absorption than immediate release; can improve motor fluctuations in people with later PD
Carbidopa/levodopa/ entacapone (Stalevo)	Initial: 1 tablet daily Maximum: 8 tablets		Refer to sections on dopamine precursors and COMT inhibitors

TABLE 2 (continued)

Drug (trade name)	Dosage	Adverse effects	Comments
MAO-B inhibitors: irreversibly and selectively inhibit brain MAO-B, reducing the breakdown of dopamine.			
Rasagiline (Azilect)	Monotherapy: 1 mg daily With levodopa: Initial: 0.5 mg daily May need to reduce levodopa dosage	Orthostatic hypotension, dyskinesias, falls, headache, nausea, angina, chest pain, syncope, depression, hallucinations, constipation, arthralgia, flu syndrome, dyspepsia	Use caution with the concomitant use of cyclobenzaprine, dextromethorphan, methadone, propoxyphene, St. John's wort or tramadol
Selegiline	Initial: 5 mg daily Dose early in the day For patients receiving levodopa/carbidopa, may start with 2.5 mg daily and then increase gradually to 5 mg twice daily Maximum: 10 mg/d	Headache, dizziness, nausea, hallucinations, confusion, vivid dreams, dyskinesias, dry mouth	Use caution with the concomitant use of cyclobenzaprine, dextromethorphan, methadone, propoxyphene, St. John's wort or tramadol; metabolized to amphetamine derivatives; contraindicated with meperidine
Miscellaneous			
Amantadine	Initial: 100 mg twice daily or 100 mg daily if receiving other PD drugs Adjustment: after 1 week on 100 mg daily, can be increased to 100 mg twice daily if necessary Maximum: 400 mg/d	Nausea, dizziness, insomnia, confusion, hallucinations, depression, livedo reticularis, orthostatic hypotension	Do not discontinue abruptly; dosing adjustment needed in renal impairment

COMT, catechol-O-methyl transferase; MAO-B, monoamine oxidase B; PD, Parkinson's disease.

- Recommend against the use of typical antipsychotic drugs (such as phenothiazines and butyrophenones) due to the risk of exacerbating motor symptoms.
- Be aware that olanzapine should not be routinely considered, quetiapine may be considered, and clozapine may be considered, but registration with a mandatory monitoring scheme is required. Note: Few specialists caring for people with PD have experience with clozapine.

(C62-C70).

Dementia

Recommendations. In the management of patients with PD and dementia, pharmacists should do the following:

- Recommend the discontinuation of potential aggravators such as anticholinergics,

amantadine, tricyclic antidepressants, benzodiazepines, tolterodine and oxybutynin.

- Recommend donepezil for the treatment of dementia in PD.
- Recommend rivastigmine for the treatment of dementia in PD or dementia with Lewy bodies.

(C71-C73).

Sleep disorders

Recommendations. In the management of patients with PD and sleep disorders, pharmacists should do the following:

- Take a full sleep history from patients who report sleep disturbance.
- Educate patients on good sleep hygiene including
  - the avoidance of stimulants (e.g., coffee, tea, caffeine) in the evening;

- the establishment of a regular pattern of sleep;
- comfortable bedding and temperature;
- the provision of assistive devices, such as a bed lever or rails to aid with moving and turning, allowing the person to get more comfortable; and
- the restriction of daytime naps.
- Recommend regular and appropriate exercise to induce better sleep.
- Review all medications and recommend the discontinuation of any drugs that may affect sleep or alertness or may interact with other medications (e.g., selegiline, antihistamines, H₂ antagonists, antipsychotics, and sedatives).
- Advise against driving or other potential occupational hazards in patients who have a sudden onset of sleep. Adjust medications to reduce this occurrence.

(C74, C75, C77).

Autonomic dysfunction

Recommendations. In the management of patients with PD and autonomic dysfunction, pharmacists should do the following:

- Refer and assist in the appropriate treatment for the following autonomic disturbances:
  - urinary dysfunction,
  - weight loss,
  - dysphagia,
  - constipation,
  - erectile dysfunction,
  - orthostatic hypotension,
  - excessive sweating, and
  - sialorrhea (hypersalivation).

For urinary dysfunction, pharmacists should do the following:

- Recommend general measures for treating urinary urgency and incontinence including avoiding coffee before bedtime and limiting water ingestion before bedtime, among others.
- Recommend peripherally acting anticholinergic drugs as options for drug therapy.

For constipation, pharmacists should do the following:

- Recommend general measures for treating gastrointestinal motility problems in PD. These can include dietary modifications and the use of laxatives, among others.
- Recommend reducing or discontinuing drugs with anticholinergic activity.
- Recommend domperidone for drug therapy.

For orthostatic hypotension, pharmacists should do the following:

- Recommend general measures including
  - avoiding aggravating factors such as large meals, alcohol, exposure to a warm environment, and drugs known to cause orthostatic hypotension, such as diuretics or antihypertensive drugs. Levodopa and dopamine agonists may also induce orthostatic hypotension.
  - increasing salt intake in symptomatic orthostatic hypotension.
  - head-up tilt of the bed at night.
  - wearing elastic stockings.
  - highlighting postprandial effects. In some patients, only postprandial hypotension occurs. Educate patients about this effect, and recommend frequent small meals.
- Recommend midodrine and fludrocortisone as options for drug therapy.

For erectile dysfunction, pharmacists should do the following:

- Recommend sildenafil for drug therapy.

(C79-C84).

Parkinson Society Canada

The PD guidelines for pharmacists were developed in collaboration with Parkinson Society Canada. Parkinson Society Canada is a national, not-for-profit, voluntary-driven organization dedicated to improving the lives of Canadians living with PD through its regional partners and 240 chapters. It provides education support and advocacy as well as funds innovative research. Health care professionals can access the CGPD and other resources at www.parkinsonclinicalguidelines.ca. Information on the National Research Program and extensive resources for patients and caregivers can be found online at www.parkinson.ca. An update on the CGPD is expected for summer 2015, with an updated guideline for pharmacists planned for 2016. ■

From the University of Waterloo School of Pharmacy, Waterloo, Ontario. Contact t5patel@uwaterloo.ca.

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References

1. Guttman M, Kish SJ, Fufkawa Y. Current concepts in the diagnosis and management of Parkinson's disease. *CMAJ* 2003;168:293-301.
2. Lang AE, Lozano AM. Parkinson's disease: first of two parts. *N Engl J Med* 1998;339:1044-53.
3. Lang AE, Lozano AM. Parkinson's disease: second of two parts. *N Engl J Med* 1998;339:1130-43.
4. Parkinson Society Canada. Parkinson's disease: social and economic impact. Available: www.parkinson.ca/site/c.kgLNiWODKpF/b.5184077/k.CDD1/What_is_Parkinsons.htm (accessed Jan. 26, 2014).
5. Guttman M, Slaughter PM, Theriault ME, et al. Burden of parkinsonism: a population-based study. *Mov Disord* 2003;18:313-9.
6. Perepelkin J. Public opinion of pharmacists and pharmacist prescribing. *Can Pharm J (Ott)* 2011;144:86-93.
7. Grimes D, Gordon J, Snelgrove B, et al. Canadian guidelines on Parkinson's disease. *Can J Neurol Sci* 2012;39 Suppl 4:S1-30. Available: www.parkinsonclinicalguidelines.ca/sites/default/files/PD_Guidelines_2012.pdf (accessed Feb. 6, 2014).
8. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology* 2009;72(Suppl 4):S1-136.
9. Lexi-Comp Inc. *Lexi-Comp online*. Hudson (OH): Lexi-Comp Inc.; 2014. Available: <http://online.lexi.com/lco/action/home/> (accessed Jan. 29, 2014).