MEDICATIONS TO TREAT PARKINSON'S DISEASE

Parkinson Canada

A message from our President and CEO

You know that managing medications for Parkinson's is complex. You need up-to-date information to treat Parkinson's and prepare for conversations with your healthcare team.

I hope you'll find this guide helpful.

I'm very proud to work with caring and dedicated donors to bring you resources like this. Donors like you make timely information, support, and hope possible for Canadians living with Parkinson's.

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Please contact us at 1-800-565-3000 or www.parkinson.ca if you have questions about managing Parkinson's, or if you or someone you love needs help.

We are always here for you, *No Matter What.*

Karen Lee
President and CEO
Parkinson Canada

This second print edition of Medications to Treat Parkinson's Disease is made possible thanks to an unrestricted education grant from Sunovion Pharmaceuticals Canada.

The purpose of this booklet is to provide healthcare professionals with a concise, yet comprehensive overview of the medications used to treat both the motor and non-motor symptoms of Parkinson's disease.

This booklet provides a brief description of pharmacological action (mechanisms of action) of the drugs as well as dosing recommendations, overview of the common and relevant adverse effects, potential interactions with foods and/or other drugs, and other practical information relevant to the treatment of persons with Parkinson's disease. Finally, also included are some helpful tools to provide patients for tracking dosing of medications, and occurrence of adverse effects.

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Brief introduction to Parkinson's disease

Pathophysiology

Of all the neurological conditions, Parkinson's disease is the fastest growing. Globally, between 1990 and 2016, the number of individuals affected with Parkinson's disease increased by 2.4 times. [1] Canada has the highest prevalence rates, estimated at an age standardized prevalence of 170 – 179 per 100,000 population.[1] Parkinson's disease is a chronic progressive neurological disorder caused by the extensive loss of dopaminergic neurons in the pars compacta of the substantia nigra, with a resulting loss of dopamine.[2,3] As dopaminergic neurons degenerate over time, several compensatory mechanisms delay the onset of motor symptoms until >60% of dopaminergic neurons are lost. However, ongoing loss of dopamine produces the highly recognizable motor symptoms of Parkinson's disease. [2] Additionally, dorsal motor nucleus and olfactory regions, cholinergic neurons of the nucleus basalis of Meynert, norepinephrine neurons of locus coeruleus, serotonin neurons of the midline raphe and neurons in the cerebral cortex, brainstem, spinal cord and peripheral autonomic nervous system are also involved in the pathology and give rise of the non-motor symptoms experienced by persons with Parkinson's disease. [2,3]

Clinical presentation

Early motor presentation of PD is characterized by bradykinesia, unilateral or asymmetric resting tremor, and rigidity. A person who presents with two of these three characteristics likely has PD, although the most widely accepted diagnostic criteria indicates that a person who presents with bradykinesia and at least one of the following, muscular rigidity, resting tremor and postural instability meets the diagnostic burden of PD. [3]. PD is less likely if early

postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction), autonomic dysfunction (characterized by urinary dysfunction/incontinence, fecal incontinence, urinary retention requiring catheterization, persistent erectile failure or orthostatic hypotension), early and prominent dementia, impaired eye movements, rapid progression and poor response to dopaminergic therapy are present; in particular, atypical Parkinsonism should be investigated if patients present with the following clinical features within the first three years of diagnosis: falls at presentation and early in the disease course, poor response to levodopa, symmetrical presentation at onset of motor symptoms, rapid progression and autonomic dysfunction. [4,5]

Many persons with PD will present with non-motor symptoms of PD. [2,3] Hyposmia, fatigue, depression, constipation and rapid eye movement sleep behaviour disorder may present several years before motor symptoms are evident or visible while psychiatric disturbances, sialorrhea, urinary urgency, sexual dysfunction and cognitive impairment are late symptoms. [2,3,4,5,6,7]

Pharmacotherapy for Parkinson's disease

The decision to initiate drug therapy for the treatment of PD as well as the choice of drug must be individualized based on patient age, severity of presenting symptoms, comorbidities, functional impairment, patient employment and patient preference. [3,4,5,8]. Some patients may opt to delay initiation of medication if there is no functional impairment due to PD.

Medications from six different pharmacological classes are commonly used to treat the motor symptoms of PD. These include, in alphabetical order, anticholinergic agents, catecholamine-O-methyl transferase (COMT) inhibitors, dopamine agonists, dopamine precursors, monoamine oxidase inhibitors and N-methyl-D-aspartate (NMDA) antagonists.

All of these classes can be initiated as monotherapy at the early stage however, the choice of the agent, as indicated earlier, will depend on patient age, clinical presentation and severity of symptoms, as well as the history of clinical effects, both benefit and adverse effects of previously tried medications. Although anticholinergic agents (e.g. benztropine, trihexyphenydyl) are used for controlling tremor, they have limited efficacy and should not be considered drugs of first choice. Use of these agents is typically limited to younger patients with PD due to a high risk for adverse effects, such as confusion and memory impairment, among the elderly. [4,5] Similarly, non-ergot dopamine agonists (e.g. pramipexole and ropinirole) are preferred in comparison to ergot-derived dopamine agonists (e.g. bromocriptine) due to adverse effects such as serosal membrane fibrosis and erythromelalgia. [4,5] Therefore, although dosing recommendations are provided for all pharmacological classes used in the treatment of PD, the factors mentioned above must also be considered upon initiation of pharmacotherapy.

I. Anticholinergic agents

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Mechanism of action

Anticholinergic agents are muscuranic receptor antagonists who's postulated to produce their pharmacological activity by decreasing the cholinergic tone in the central nervous system by modulating the cholinergic interneurons, thereby potentially correcting an imbalance between dopamine and acetylcholine that occurs in PD, although the mechanism has not been elucidated completely. [9]

Generic names (Brand names)	Formulations available [10]	Common starting, usual and maximum doses [11, 12, 13, 14]	Adverse effects [11,12,13]	Comments
Benztropine	Marketed Solution: 1mg/ml Tablets: 1mg Dormant or approved but not marketed Tablets: 2mg	**Initial dose:** 0.5-1mg QHS **Titration:** increase by 0.5mg every 5-6 days **Usual dose:** 1 – 2 mg BID **Maximum dose:** 2 mg TID	• Blurred vision • Dry mouth • Constipation • Nausea/vomiting • Urinary retention • Sedation • Confusion • Hallucination • Memory loss • Dizziness • Orthostatic hypotension • Tachycardia	• Not agents of first choice in the treatment of PD; only used for management of problematic tremor [4,5] • Modest benefit for the tremor-predominant presentation of PD • Use generally limited to younger persons as anticholinergic adverse effects may be problematic for older persons [4,5,12] • Counteracts benefits of cholinesterase inhibitors (donepezil, rivastigmine and galantamine) used in the treatment of cognitive disorders such as Parkinson's disease dementia [4,5] • Increases the anticholinergic side effects when used with other anticholinergic drugs (e.g., urinary anticholinergics, tricyclic antidepressants, etc.) [4,5]
Trihexyphenidyl	Marketed: none Dormant or approved but not marketed 5mg tablets	**Initial dose:** 1 mg daily QHS **Titration:** may increase by 2mg every 3-5 days **Usual dose:** : 6 – 10mg per day in divided doses (2mg TID to 5mg BID)		
Procyclidine	Marketed: none Dormant/Approved: 2.5 and 5mg tabs 2.5mg/5ml elixir	**Initial dose:** 2.5mg TID after meals; titrate gradually to 5mg TID **Usual dose:** 2.5-5mg TID and QHS **Maximum dose:** 30mg per day		

II. Catechol-o-methyl transferase (COMT) inhibitors

Mechanism of action

Catechol-O-methyl-transferase (COMT) inhibitors slow, or prevent the breakdown of levodopa in the peripheral tissues, allowing for more levodopa to be available in the brain to be converted to dopamine. [9]

Generic names (Brand names)	Formulations available [10]	Common starting, usual and maximum doses [3,11,12,13,14]	Adverse effects [13,14]	Comments
Entacapone (Comtan)	200 mg tablets **DO NOT CRUSH**	**Initial dose:** 200mg with each levodopa dose **Usual dose:** 200mg three – four times daily **Maximum dose:** 8 tablets (1600mg) daily	• Postural Hypotension • Fatigue, pain • Profuse diarrhea (can be delayed) • Dyskinesia • Urine discoloration (brown-orange) • Orange stain to teeth if tablets are bitten • Nausea/vomiting • Constipation • Agitation (rare) • Changes in liver function (rare) • Dizziness • Agitation (rare) • Abdominal pain • Hallucinations	• Useful only when given with levodopa to prolong duration of action and prevent "wearing off" [3] • To avoid dyskinesia or psychosis reduce levodopa dose by 10 - 30% when entacapone is started. [13,14] Patients using levodopa/benserazide combination may require a larger dose reduction than those using levodopa/carbidopa combination [13] • Alternatively, add entacapone gradually to one or two of the levodopa doses based on when "wearing off" symptoms typically occur [15] • Advise patients to refrain from taking multiple Stalevo tablets together since only 200mg entacapone can be taken at one time • Do not break or crush Stalevo tablets. Stalevo doses cannot be fractionated [14] • Titrate dose of Stalevo to optimize therapeutic response from levodopa [13,14] • Dosing can be optimized by adjusting dose and/or dosing interval [14]
Entacapone + Levodopa + Carbidopa (Stalevo)	Tablets in combination with levodopa Five available strengths (entacapone dose/carbidopa dose/levodopa dose): - 50/12.5/200mg - 75mg/18.75/200mg - 100/25/200mg - 125/31.25/200mg - 150/37.5/200mg **DO NOT CRUSH**	**Initial dose:** Current L-dopa dose the patient is taking **Usual dose:** 50mg – 150mg twice daily **Maximum dose:** 8 tabs/day (for all strengths)		

***Tolcapone (Tasmar)** is a central and peripheral COMT inhibitor that is only available through Health Canada's Special Access Program due to increased risk of liver damage.
****Opicapone (Ongentys)** is another COMT inhibitor, dosed once daily, that is FDA approved but not currently available in Canada (at time of publication).

III. Dopamine agonists (DA)

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Mechanism of action

Dopamine agonists are synthetic dopamine receptor agonists and therefore, simulate dopamine's action in the brain. [9]

Generic names (Brand names)	Formulations available	Common starting, usual and maximum doses [3,11,12,13,14]	Adverse effects [4,5,13,14]	Comments
Bromocriptine	Tablets (2.5mg) and capsules (5mg)	**Initial dose:** 1.25mg BID **Titration:** Increase by 1.25 – 2.5mg every 2 - 4 weeks as necessary to clinically effective dose (Slow dose titration to minimize nausea and dizziness) **Usual dose:** 5 – 10mg TID **Maximum dose:** 10mg TID	• Dizziness • Sleepiness • Fatigue • Headache • Blurred vision • Psychosis • Constipation • Nausea • Weakness • Rhinitis • Serious pulmonary and cardiac valve fibrosis (rare)	• Dopamine agonists are associated with higher prevalence of hallucinations, excessive daytime somnolence and impulse control disorders in comparison to levodopa [4,5] • Bromocriptine is an ergot derivative and should not be considered as the dopamine agonist of first choice due to serious pulmonary and cardiac valve fibrosis. [4,5] • Baseline and annual erythrocyte sedimentation rate (ESR), renal function, cardiac echocardiogram and chest x-ray are required if treating with bromocriptine. [4,5] • Dopamine agonists can reduce off-time by about 1.5 – 2 hours per day when used with levodopa and may allow for a dose reduction of levodopa • Never stop DA suddenly to avoid withdrawal symptoms such as panic attacks, sweating, dysphoria, pain, and craving for DA • Avoid rotigotine patch and apomorphine film if patient has sulfite allergy sensitivity (more common in patients with asthma) [13] • With rotigotine patches should be applied every 24 hours [4,5] • Avoid placing the rotigotine patch in the same location twice within 14 days to prevent skin irritation [4,5]. Patch may be applied on abdomen, shoulder, upper arm, thigh, hip or flank [13]

III. Dopamine agonists (DA) (continued)

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Generic names (Brand names)	Formulations available	Common starting, usual and maximum doses	Adverse effects	Comments
Pramipexole (Mirapex)	Tablets (0.125mg,0.25mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg) (Mirapex only available in 0.125 and 0.25mg tablets) **Extended release formulations are not available in Canada**	**Initial dose:** 0.125mg three times a day; twice daily if CrCL 30-50mL/min; once daily if CrCL 15-30mL/min; increase every 7 days **Titration:** 0.125 – 0.25mg every 7 days (Slow dose titration to minimize nausea and dizziness) **Usual dose:** 0.5-1.5mg three times a day **Maximum dose:** 1.5mg three times per day **Renal dysfunction dosing:** **CrCl:** 30 – 50ml/min **Initial:** 0.125mg twice daily **Maximum:** 0.75mg three times daily **CrCl:** <30ml/min **Initial:** 0.125mg once daily **Maximum:** 1.5mg once daily	• Orthostatic hypotension • Severe drowsiness may affect driving ability; sleep disorders including sudden onset of sleep • Headache • Psychosis • Hallucinations • **Impulse control disorders (ICDs)** • Leg edema • Nausea	• Dopamine agonists are associated with higher prevalence of hallucinations, excessive daytime somnolence and impulse control disorders in comparison to levodopa [4,5] • Bromocriptine is an ergot derivative and should not be considered as the dopamine agonist of first choice due to serious pulmonary and cardiac valve fibrosis. [4,5] • Baseline and annual erythrocyte sedimentation rate (ESR), renal function, cardiac echocardiogram and chest x-ray are required if treating with bromocriptine. [4,5] • Dopamine agonists can reduce off-time by about 1.5 – 2 hours per day when used with levodopa and may allow for a dose reduction of levodopa • Never stop DA suddenly to avoid withdrawal symptoms such as panic attacks, sweating, dysphoria, pain, and craving for DA • Avoid rotigotine patch and apomorphine film if patient has sulfite allergy sensitivity (more common in patients with asthma) [13] • With rotigotine patches should be applied every 24 hours [4,5] • Avoid placing the rotigotine patch in the same location twice within 14 days to prevent skin irritation [4,5]. Patch may be applied on abdomen, shoulder, upper arm, thigh, hip or flank [16]

III. Dopamine agonists (DA) (continued)

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Generic names (Brand names)	Formulations available	Common starting, usual and maximum doses	Adverse effects	Comments
Ropinirole (Requip)	0.25mg, 1mg, 2mg, 5mg tablets **Extended Release formulations not available in Canada**	**Initial dose:** 0.25mg three times daily **Titration:** For doses up to 3mg/day, increase dose by 0.75mg every 7 days. For doses 3 to 9 mg/day, increase dose by 1.5mg every 7 days; for doses above 9mg/day, increase dose by 3mg every 7 days Slow down dose titration to minimize adverse effects **Usual dose:** 12 – 16mg/day **Maximum dose:** 8mg three times per day	• Orthostatic hypotension • Severe drowsiness may affect driving ability; sleep disorders including sudden onset of sleep • Headache • Psychosis • Hallucinations • **Impulse control disorders (ICDs)** • Leg edema • Nausea	• Dopamine agonists are associated with higher prevalence of hallucinations, excessive daytime somnolence and impulse control disorders in comparison to levodopa [4,5] • Bromocriptine is an ergot derivative and should not be considered as the dopamine agonist of first choice due to serious pulmonary and cardiac valve fibrosis. [4,5] • Baseline and annual erythrocyte sedimentation rate (ESR), renal function, cardiac echocardiogram and chest x-ray are required if treating with bromocriptine. [4,5] • Dopamine agonists can reduce off-time by about 1.5 – 2 hours per day when used with levodopa and may allow for a dose reduction of levodopa • Never stop DA suddenly to avoid withdrawal symptoms such as panic attacks, sweating, dysphoria, pain, and craving for DA • Avoid rotigotine patch and apomorphine film if patient has sulfite allergy sensitivity (more common in patients with asthma) [13] • With rotigotine patches should be applied every 24 hours [4,5] • Avoid placing the rotigotine patch in the same location twice within 14 days to prevent skin irritation [4,5]. Patch may be applied on abdomen, shoulder, upper arm, thigh, hip or flank [13]
Rotigotine (Neupro)	Patch (1mg/24hour, 2mg/24hour, 3mg/24 hour, 4mg/24 hour, 6mg/24 hour, and 8mg/24 hour)	**Early-stage** **Initial dose:** 2mg/24 hour patch once daily; **Titration:** Increase by 2mg/24hours every 7 days **Usual dose:** 4-6mg daily **Maximum dose:** 6mg/24 hours **Advanced-stage** **Initial dose:** 4mg/24 hour patch **Titration:** 2mg/24 hour patch every 7 days **Maximum:** 16mg/24 hours When discontinuing rotigotine, decrease by 2mg/24 hour patch every 7 days		

III. Dopamine agonists (DA) (continued)

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Generic names (Brand names)	Formulations available	Common starting, usual and maximum doses	Adverse effects	Comments
Apomorphine (Movapo, Kynmobi)	Pre-filled pens (30mg/3ml) (Movapo) Ampoules (approved but not currently marketed in Canada) (20mg/2mL) (Movapo) Sub-lingual Films (10mg, 15mg, 20mg, 25mg, and 30mg) (Kynmobi)	**Sub-cutaneous injection:** **Initial Dose:** 0.2mL (2mg), may titrate to 6mg (max: 5 doses or 20mg/day) **Usual Dose:** 0.2mL (2mg) – 0.4mL (4mg) three times per day **Maximum Dose:** 0.6mL (6mg) per day Doses have to be administered by healthcare professionals and dosing adjusted based on response under the supervision and observation of healthcare professionals. **Film:** **Initial Dose:** 10mg PRN at intervals of ≥2 hours for "off episodes" up to maximum dose of 5 doses per day **Titration:** Increase dose in 5mg increments every 3 days if required based on response and adverse effects. **Maximum**: single dose of 30 mg at intervals ≥2 hours and a maximum of 5 doses per day	**Subcutaneous Apomorphine:** • Injection site reactions • Rhinorrhea **Sublingual Apomorphine:** • Oral/pharyngeal tissue swelling and/or • Oral/pharyngeal tissue pain/paraesthesia **General** • Dyskinesia • Chest pain • Dizziness • Somnolence • Hallucinations • Confusion • Nausea • Vomiting • Falling/syncope • Severe drowsiness may affect driving ability; sleep disorders including sudden onset of sleep	• Apomorphine is only for PRN (as needed) use in extreme cases of sudden severe "off" symptoms. [13] • Apomorphine is not recommended for elderly patients due to profound hypotension that requires monitoring by specialized movement disorders centres • Apomorphine can cause severe nausea and vomiting, so domperidone pre-treatment for two days prior to the initial dosage of apomorphine is required [13] • Do not use in person with sulfite hypersensitivity [13,14] • Concomitant use of antihypertensives and vasodilators can increase the hypotensive effects of apomorphine. Use of Kynmobi is cautioned in those who are on antihypertensives, vasodilators and alcohol while the concomitant use of Movapo and antihypertensives and vasodilators is contraindicated [13,14] • Concomitant use of 5HT3 antiemetics (granisetron, ondansetron) due to profound hypotension [13, 14] • The film form of apomorphine is to be delivered sublingually and should not be cut, chewed, or swallowed

Additional notes about dopamine agonists

Impulse Control Disorders

Dopamine agonists (DA) may result in impulse control disorders (ICDs). Although any dopaminergic medication increases the risk of ICDs, dopamine agonists present the greatest risk. ICDs are evident when individuals cannot resist the drive to behave in ways that can have negative impacts psychosocially. Symptoms of such disorders include any uncontrolled, or compulsive behaviours (e.g. uncontrolled eating, shopping, gambling, sexual urges). The literature reports that approximately 20% of patients treated with DA develop ICDs. [5,16] Patients most at risk for ICD include treatment with dopamine agonists, levodopa, younger individuals, aged 65 years old or less, unmarried, with a family history of gambling and ongoing cigarette smoking, functional impairment, depression, anxiety, obsessive-compulsive disorders, impulsivity and novelty-seeking. [16] ICDs can lead to significant financial and social disruption, but are usually reversible with dose reduction or discontinuation. [16] Patients and family members should be instructed to watch for ICDs prior to initiation of DA treatment. [5] Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS) screens for compulsive gambling, sex, buying, eating, hobbyism, punding (repetitive motor behaviour) and intentional over medication. [17, 18]

Dopamine agonist withdrawal syndrome

Patients experience a range of symptoms when dopamine agonists are being withdrawn. Some experience no symptoms while some may experience a worsening of motor control which can be managed with another dopaminergic drug. However, some patients experience physical and psychological symptoms upon the withdrawal of dopamine agonists. These symptoms include anxiety, panic attacks, dysphoria, diaphoresis, pain, orthostatic hypotension, and drug cravings. [19] Up to 19% of patients may experience dopamine-agonist withdrawal syndrome (DAWS). Withdrawal symptoms are more common in patients with ICDs or with increasing cumulative exposure at $\geq$ 1.5mg/day of pramipexole, $\geq$7.5mg/day of ropinirole or $\geq$5mg of rotigotine. [19] The management involves a slower tapering schedule and closer monitoring of high risk patients for DAWS. [19] As with ICDs, patients and caregivers should be made aware of DAWS. [19]

Additional notes about dopamine agonists (continued)

Adverse effects

The adverse effects of dopamine agonists are generally similar to those associated with levodopa. However, certain side effects, such as excessive daytime sleepiness, visual hallucinations, confusion and swelling of the legs, occur more commonly with the use of dopamine agonists than with levodopa. Elderly people with PD are more likely than younger people to have these troublesome adverse effects and should be avoided in patients older than 70 years of age. [5]

IV. Levodopa (Dopamine Precursor)

Mechanism of action

Dopamine is unable to cross the "blood brain barrier"; thus, if administered peripherally, it will produce peripheral adverse effects, such as nausea and dizziness, but will not be effective in controlling the symptoms of Parkinson's disease. Levodopa is a precursor of dopamine that is able to pass through the blood brain barrier. However, levodopa is rapidly broken down in the body before it crosses the blood-brain barrier; therefore, large doses are required to produce an effect. Dopa-decarboxylase inhibitors (benserazide and carbidopa) are given concurrently with levodopa to prevent its breakdown in the periphery and therefore allow levodopa to cross the blood-brain barrier. [9]

(see chart next page)

IV. Levodopa (Dopamine Precursor)

Generic names (Brand names)	Formulations available [10]	Common starting, usual and maximum doses [13,14]	Adverse effects [13,14]	Comments
Levodopa + Carbidopa Immediate Release (IR) (Sinemet)	Tablet, 100/10, 250/25 100/25 (higher carbidopa ratio is preferred)	**Initial dose:** ½ tablet of 100/25 BID - TID with non-protein snack. Increase by 50/12.5 - 100/25 every 3 – 7 days **Usual dose:** 100/25mg three to four times daily to every 3 – 4 hours during the day (Usual dose is patient dependent) **Maximum dose:** No upper limit; adverse effects and motor complications may limit dose Slow titration to prevent nausea, dizziness **May crush and take with carbonated drink to speed onset**	• Hallucinations • Nausea/Vomiting • Confusion • Dizziness • Vivid dreams • Fatigue • Orthostatic hypotension • Dyskinesias • Sudden onset of sleep • Psychotic episodes	• Protein or iron ↓ bioavailability [14] • Constipation & Anticholinergics agents ↓ GI motility – delays onset [12] • Hypotension with concomitant use of antihypertensive agents due to potential risk of additive hypotension with concurrent use of levodopa [13,14] • Controlled release formulations are rarely used during the day due to erratic absorption which results in delayed & unpredictable onset • Bioavailability is about 70% of immediate release [5] • **Very rare:** risk of neuroleptic malignant syndrome if stopped abruptly [5] • DUODOPA® should only be prescribed by neurologists who are experienced in the treatment of patients with Parkinson's disease, and who have completed the DUODOPA® education program that includes training in: the criteria for selecting suitable patients; initiation and management with DUODOPA® therapy via naso-intestinal infusion and percutaneous endoscopic gastrostomy; postprocedural care; and, the risks associated with the procedure and long-term use of the PEG-J. • The use of DUODOPA gel, delivered via a J-tube continuously to the intestines, may be used to produce stable levels of levodopa throughout the day to reduce the motor fluctuation of wearing off and dyskinesia. [5]

IV. Levodopa (Dopamine precursor) (continued)

Generic names (Brand names)	Formulations available	Common starting, usual and maximum doses	Adverse effects	Comments
Levodopa+ Benserazide (Prolopa)	Capsules (50/12.5, 100/25, 200/50)	**Initial Dose:** 50/12.5mg twice daily; increase every 3 – 7 days **Usual dose:** 100/25mg three to four times daily to every 3 – 4 hours during the day (Usual dose is patient dependent) **Maximum dose:** No upper limit; adverse effects and motor complications may limit dose Slow titration to prevent nausea, dizziness **May crush and take with carbonated drink to speed up onset**	• Hallucinations • Nausea/ Vomiting • Confusion • Dizziness • Vivid dreams • Fatigue • Orthostatic hypotension • Dyskinesias • Sudden onset of sleep • Psychotic episodes	**SEE PREVIOUS PAGE** [Levodopa+Carbidopa Immediate Release (IR) (Sinemet)]
Levodopa Carbidopa Controlled Release (CR)	Tablets 100/25, 200/50 **DO NOT CRUSH**	100/25 to 200/50 at bedtime to prevent symptoms at night or morning wearing off		
Levodopa+ Carbidopa (DUODOPA)	Intestinal gel Levodopa: 20ml/ml Carbidopa:5mg/mL	40–120 mg/hour for 16 hours		
Entacapone+ Levodopa + Carbidopa (Stalevo)	Tablets in combination with Levodopa Five available strengths (Entacapone dose/ Carbidopa dose/Levodopa dose): • 50/12.5/200mg • 75mg/18.75/200mg • 100/25/200mg • 125/31.25/200mg, • 150/37.5/200mg **DO NOT CRUSH**	**Initial Dose:** Current L-dopa dose the patient is taking **Usual dose:** 50mg – 150mg twice daily **Maximum dose:** 8 tabs/day (for all strengths)		

V. MAO-B Inhibitors

Mechanism of action

These drugs prevent the breakdown of dopamine in the brain by preventing the actions of the enzyme MAO-B. This results in increased concentration of dopamine that is ready for use in the nerve cells. [12].

Generic names	Formulations available [10]	Common starting, usual and maximum doses [13,14]	Adverse effects [13,14]	Comments
Rasagiline (Azilect)	Tablets (0.5 mg, 1 mg)	**Initial dose:** 0.5 mg daily **Usual dose:** 1mg daily **Maximum dose:** 1 mg daily Reduce dose if liver disease	• Dizziness • Headache • Weight loss • Constipation • Postural hypotension • Nausea/vomiting • Dyskinesias These agents are usually well tolerated; however, in the rare case, they may increase blood pressure significantly.	• Monoamine oxidase B inhibitors, as with all other dopaminergic agents, may exacerbate the potential adverse effects associated with the use of other dopaminergic medications. • Need to discontinue 2 weeks prior to elective surgery if receiving anaesthesia • Rasagiline can be used alone for early stage and as an "add-on" with dopaminergic drugs for late stage for reduction of "off" time [5] • No specific diet for both monoamine oxidase B inhibitors restriction except to avoid aged cheese with tyramine > 150mg/day

V. MAO-B Inhibitors (continued)

Generic names (Brand names)	Formulations available	Common starting, usual and maximum doses	Adverse effects	Comments
Selegiline (Eldepryl)	Tablets (5mg)	**Initial dose:** 2.5–5 mg daily **Usual dose:** 5mg two times daily with meals, every morning and at noon with meals **Maximum dose:** 5mg twice daily every morning and noon with meals	• Confusion • Dizziness • Lightheadedness/fainting • Insomnia, especially if second dose is taken later in the day. Take second dose no later than at noon • Hallucinations • Intense dreams • Headaches • Nausea • Abdominal pain • Dry mouth • Weight loss • Dyskinesias • Orthostatic hypotension	• Monoamine oxidase B inhibitors, as with all other dopaminergic agents, may exacerbate the potential adverse effects associated with the use of other dopaminergic medications. • Need to discontinue 2 weeks prior to elective surgery if receiving anaesthesia • Selegiline is used as adjunctive treatment to reduce wearing off [5] • Rasagiline can be used alone for early stage and as an "add-on" with dopaminergic drugs for late stage for reduction of "off" time [5] • No specific diet for both monoamine oxidase B inhibitors restriction except to avoid aged cheese with tyramine > 150mg/day
Safinamide (Onstryv)	Tablets (50mg and 100mg)	**Initial dose:** 50mg once per day. Increase by 50mg in 2 weeks if required **Usual Dose:** 50-100mg daily **Maximum Dose:** 100mg daily Maximum dose for patients with hepatic impairment (Child-Pugh B) is 50mg/day Contraindicated in severe hepatic impairment.	• Dyskinesias • Nausea • Insomnia • Dizziness • Falls • Confusion • Hallucinations • Orthostatic hypotension • Hypertension (more common than orthostatic hypotension)	• Take Safinamide in the evening if experiencing drowsiness. Avoid Safinamide if any problem with retina such as diabetic retinopathy. • Salfinamide is only used as an "add-on"for late stage. • When discontinuing safinamide, taper down by 50mg for 7 days before stopping [13]

VI. NMDA Antagonist

Mechanism of action

The mechanism of action of amantadine in the treatment of Parkinson's disease is not fully elucidated. As a NMDA receptor antagonist, it is thought to reduce dyskinesia. It has mild anti-parkinsonian action in addition. [9]

Generic names (Brand names)	Formulations available	Common starting, usual and maximum doses	Adverse effects	Comments
Amantadine	Capsule (100mg) and syrup (50mg/5mL)	**Initial Dose:** 100mg once daily; increase every 7 days **Usual Dose:** 100mg twice to three times daily in the morning, noon and early afternoon **Maximum Dose:** 200mg twice daily **Reduce dose if renal dysfunction**	• Anticholinergic side effects (blurred vision, dry mouth, difficulty with urination, constipation, cognitive impairment) • Dizziness • Insomnia if taken later in the day • Nightmares • Confusion • Hallucinations • Peripheral edema • Nausea • Orthostatic hypotension • Livedo reticularis (red-purple discolouration of the skin; occurs in <1%)	• Older adults are especially at risk for anticholinergic adverse effects, hallucinations and edema in lower extremities [5,12] • Reduce dose of amantadine if patient has decreased creatinine clearance • Never discontinue amantadine suddenly; always taper off

Treating Parkinson's disease with Dopaminergic Medications: Clinical Pearls

- It is best to start with low doses of medications and gradually increase dose if needed.
- Have the patient keep a medication/mobility diary to record when they take their medication and when they experience adverse effects or wearing off, so that you can best adjust dosing of their medication.
- Encourage the use of compliance packaging (for e.g. blister pack, pill boxes, dosette) and multiple alarms on a watch/mobile phone to help patients remember to take their medications on time.
- Assess the patient's ability to swallow, as this can be impaired by Parkinson's disease. Some medications cannot be crushed. If required, levodopa suspension can be prepared.
- Dietary protein competes with levodopa for absorption; therefore, advise patients to avoid meals high in protein content. If patients complain of delayed onset or variability in effect, advise patients to take levodopa ½ - 1 hour before meal or protein rich food such as milk, eggs or peanut butter.
- To reduce severe nausea, improve gastric motility and to speed up levodopa's onset of action, domperidone can be given prior to each dose. The dose of domperidone should be limited to 30mg/day due to the risk of QT interval prolongation resulting in ventricular arrhythmias or sudden cardiac death, particularly in elderly patients.
- Since all PD medications can cause side effects of dizziness and fatigue or drowsiness, patients should be advised to keep alcohol intake minimal.
- If a patient is admitted to a hospital, family must provide hospital staff with the exact times of day medications are to be administered so doses are given on the same schedule the patient follows at home, not hospital schedule. Provide staff also with a list of medications that are contraindicated in PD as if patients are allergic to them. Prior to surgery, patients should take the first

dose of PD medication early in the morning with sips of water. If prolonged "npo" is required, rectal levodopa formulation may be required. (see appendix) If patient is on entacapone or Stalevo, educate staff not to be alarmed by patient's orange-brown urine discoloration.

- Do not substitute Parkinson's medications.
- Resume medications immediately following procedures, unless vomiting or severely incapacitated.
- If an antipsychotic is necessary, use quetiapine or if not effective, then clozapine
- Ambulate as soon as medically safe. Patients may require assistance.
- Management of selected motor complications and selected side effects.

Common interactions with other drugs and food

- Concurrent use of dopaminergic use with other dopaminergic agents will increase the occurrence of dopaminergic adverse effects.
- Avoid medications that worsen symptoms of Parkinson's disease, especially antipsychotics. Only quetiapine and clozapine may be used, if absolutely required, in patients with Parkinson's disease.
- Antihypertensive and drugs with hypotensive effects (for example tricyclic antidepressants) may worsen hypotension and postural hypotension in patients with Parkinson's disease. Use of these agents should be monitored closely, especially if using concurrently with dopaminergic drugs.
- Monitor for excessive sedation, dizziness, falls if there is concurrent use with agents that increase sedation (anticholinergic agents, antidepressants, benzodiazepines, etc).
- Review all drugs that a patient is concurrently taking to assess potential for drug interactions. The list in the table on the following page is not comprehensive:

Common interactions with other drugs and food (continued)

Parkinson Medication	Drug Interactions (may increase of decrease the effectiveness and adverse effects of dopaminergic agents) [16,17]
Levodopa-Carbidopa	Antipsychotics, antihypertensives, iron, high protein foods (or nutritional supplement), isoniazid, metoclopramide
Rotigotine	Alcohol, antidepressants, antihypertensives, antipsychotics, benzodiazepines, metoclopramide
Pramipexole	Inhibitors of renal tubular secretion (Amantadine, ranitidine, diltiazem, quinidine, quinine, ranitidine, triamterene, verapamil) may reduce the renal clearance of pramipexole and increase its' effectiveness and/or adverse effects. Monitor closely alcohol, antidepressants, antihypertensives, antipsychotics, benzodiazepines, metoclopramide
Ropinirole	Inhibitors of cytochrome P450 1A2 (Ciprofloxacin, clarithromycin, erythromycin, fluvoxamine, itraconazole, propranolol) may increase the availability of ropinirole and its effect and adverse effects. Inducers of cytochrome P450 1A2 (smoking, etc) may reduce ropinirole and its effectiveness. Monitor closely alcohol, antidepressants, antihypertensives, antipsychotics, benzodiazepines, metoclopramide
Apomorphine	Avoid use with ondansetron, and granisetron, alcohol, antidepressants, antihypertensives, antipsychotics, benzodiazepines, metoclopramide
Benztropine and Trihexyphenidyl	As anticholinergic drugs, benztropine and trihexyphenidyl may decrease the effectiveness of cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and increase the adverse effects of other anticholinergics drugs (e.g. amantadine, antipsychotics, trihexyphenidyl, tricyclic antidepressants)
Selegiline	Amphetamines, methamphetamine, atomoxetine, bupropion, buspirone, dextromethorphan, methadone, methylphenidate, pseudoephedrine (increases blood pressure)
Rasagiline	CYP1A2 inhibitor (e.g., ciprofloxacin, fluvoxamine) may increase rasagiline concentration
Safinamide	Although drugs with the potential to cause serotonin syndrome are listed as contraindicated, the potential for this interaction is low as safinamide, like rasagiline and selegiline, is monoamine oxidase B inhibitor
Entacapone	Antipsychotics, antihypertensives, Iron, high protein foods (or nutritional supplement), isoniazid, metoclopramide
Amantadine	Iron will also worsen constipation

Treatment of non-motor symptoms of Parkinson's disease (use the PD NMS Questionnaire to assess non-motor symptoms)

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Constipation	Constipation is a common non-motor symptom of Parkinson's disease and can present several decades before motor symptoms. [3,5,11,12,20] Slower transit time through the gastrointestinal tracts can impact the intestinal absorption of dopaminergic drugs. Constipation impacts other clinical outcomes such as incomplete bowel evacuation, impaction of hard stool and weight loss. [5,11] Non-pharmacological options include: [5] · Consume high fiber diet (fruits, vegetables, etc.) · Increase fluid intake · Increase physical activity · Discontinue anticholinergic drugs Pharmacological treatment [5, 11, 20] is listed below.		
	Polyethylene glycol [14]	17g in 120 – 240ml of water once daily
	Psyllium [14]	2.5 – 30g/day in divided doses
	Methylcellulose [14]	2g (1 heaping tablespoon) in 240ml water once daily to TID
	Lactulose [14]	10 – 20g (15 – 30ml) daily; may increase to 40g (60ml) daily if required
	Domperidone [14]	10mg three times daily
Depression and Anxiety	Depression and anxiety are common symptoms, reported in up to 50% of patients with PD. They may precede motor symptoms, and significantly affect a patient's functioning and quality of life. [5,11,12,20] Antidepressants are effective. Patient education is crucial to ensure medication adherence. Optimizing treatment can improve concentration, motivation, anxiety and a sense of well-being. Initiate at a low dose and titrate slowly to a usual therapeutic dose to minimize activation syndrome. Do not discontinue abruptly, taper down slowly to minimize discontinuation syndrome.	
	SSRI	
	Take with food to prevent nausea side effect. If patients report vivid dreams or act out their dreams, move dosing from evening to morning. Adverse effects include weight gain and sexual dysfunction. Watch for rare hyponatremia especially for elderly patients on concurrent diuretics. Concurrent use with antiplatelet agents increases the risk of bleeding.	

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Depression and Anxiety	**SSRI**	
	Citalopram (Celexa®) [14]	**Initial dose:** 10mg once daily **Usual dose:** 20mg once daily **Maximum dose:** 40mg once daily in older adults due to risk of QT prolongation with higher doses
	Escitalopram (Cipralex®) [14]	**Initial dose:** 5mg once daily **Usual and maximum dose:** 10mg daily Risk of QT prolongation in older adults
	Paroxetine (Paxil® IR and CR) [14]	**Initial dose:** 10mg once daily **Usual dose:** 20mg once daily **Maximum dose:** 40mg once daily Do not use paroxetine in older adults due to risk of anticholinergic adverse effects before noon
	Fluoxetine (Prozac®) [14]	**Initial dose:** 10mg once daily **Usual dose:** 20 - 60mg/day **Maximum dose:** 80mg/day Fluoxetine has a long half-life, therefore, it does not require taper when discontinuing
	Sertraline (Zoloft®) [14]	**Initial dose:** 25mg once daily **Usual dose:** 50 - 100mg/day **Maximum dose:** 200mg/day
	SNRI	
	SNRI can cause hypertension at high dosages. May cause insomnia if taken at bedtime. Other adverse effects include weight gain and sexual dysfunction. Watch for rare hyponatremia, especially in older adults on diuretics. May increase the risk of bleeding when taken concurrently with antiplatelet agents. Are often used for the treatment of chronic neuropathic pain.	
	Desvenlafaxine (Pristiq®) [14]	**Initial dose:** 50mg daily **Usual and maximum dose:** 100mg/day Dosing may need to be adjusted in renal dysfunction
	Venlafaxine (Effexor XR®) [14]	**Initial dose:** 37.5mg/day **Usual dose:** 75 – 225mg/day **Maximum dose:** 225mg/day
	Duloxetine (Cymbalta®) [14]	**Initial dose:** 30mg once daily **Usual:** 30-60mg/day **Maximum:** 120mg/day

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Depression and Anxiety	**Tri-cyclic antidepressants (TCAs)**	
	Tricyclic antidepressants are taken at bedtime as they cause sedation. Other adverse effects include anticholinergic side effects, orthostatic hypotension, cardiac conduction abnormalities, weight gain and sexual dysfunction. TCAs are used for the treatment of insomnia and chronic neuropathic pain.	
	Nortriptyline (Aventyl®) [14]	**Initial dose:** 10mg at bedtime **Usual dose:** 25mg three times daily **Maximum dose:** 150mg/day
	Amitriptyline (Elavil®) [14]	**Initial dose:** 10-25mg at bedtime **Usual dose:** 100 – 300mg/day **Maximum dose:** 300mg/day Amitriptyline is avoided in older patients because of a higher anticholinergic load
	Imipramine [14]	**Dosing:** 10-25mg at bedtime **Usual dose:** 50mg/day **Maximum dose:** 100mg/day Imipramine is avoided in older patients because of a higher anticholinergic load
	Desipramine [14]	**Dosing:** 10-25mg at bedtime **Usual dose:** 50mg/day **Maximum dose:** 100mg/day
	Other antidepressants	
	Buproprion (Wellbutrin SR and XL®) [14])	**Initial dose (IR):** 50-100mg once daily to twice daily before noon **Usual dose (IR):** 100mg three times daily **Maximum dose (IR):** 450mg/day **Initial dose (SR):** 150mg once daily **Usual dose (SR):** 150mg twice daily **Maximum dose (SR):** 200mg twice daily **Initial dose (XL):** 150mg once daily **Usual dose (XL):** 300mg once daily **Maximum dose (XL):** 450mg once daily Useful in low energy and motivation from depression. Bupropion+ PD medications may increase risk of restlessness, anxiety, gait disturbances, and dizziness because of additive dopamine agonist effect. May lower dose and monitor closely.

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Depression and Anxiety	**Mirtazapine** [14]	**Initial dose:** 7.5mg at bedtime **Usual dose:** 15 – 30mg at bedtime **Maximum dose:** 45mg at bedtime Dose with care in older adults with moderate to severe renal or hepatic impairment. Useful for stimulating appetite in older adults. Useful for the treatment of insomnia.
Pain	PD may reduce pain thresholds. Morning dystonia and muscle pain/stiffness often occur during off periods, while dyskinesia at peak drug level may also cause pain.[12] Pain that occurs during the "off" state may benefit from the adjustment of dopaminergic medications. Stretching, massage, and adjustment of PD drugs are helpful strategies. Acetaminophen is safer than NSAIDs for chronic pain in older adults.	
	Acetaminophen (Tylenol ES® or Arthritis®) [14]	**Usual dose:** 325 – 560mg TID to QID PRN. **Max dose:** 3,250mg/day for long-term use Effective for mild pain or osteoarthritis
	Duloxetine (Cymbalta®) [14]	**Initial dose:** 30mg once daily **Usual:** 30-60mg/day **Maximum:** 120mg/day
	Gabapentin (Neurontin®) [14]	**Initial dose:** 300mg at bedtime **Usual dose:** 900 – 1200mg/day in divided doses, TID Adjust dosing for declining renal function Titrate dosing to effect; taper when discontinuing Watch for respiratory depression, sedation, dizziness, fatigue and edema (legs, ankle or feet), weight gain

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Pain	**Pregabalin** (Lyrica®) [14]	**Initial dose:** 25-75mg BID to TID **Usual dose:** 300 – 600mg/day in divided doses BID - TID Adjust dosing for declining renal function Titrate dosing to effect; taper when discontinuing Watch for respiratory depression, sedation, dizziness, fatigue and edema (legs, ankle or feet), weight gain
Sialorrhea (Drooling)	Drooling is reported in up to 78% of persons with Parkinson's disease and results from inability to swallow saliva.[5,12] Non-pharmacologic treatment includes gum chewing. [5]	
	Glycopyrrolate [13]	**Dose:** 0.1mg in the morning and 0.2mg in the evening
	Atropine 1% drop [11,21,22]	Apply 1 drop/spray under the tongue twice daily as needed
	Ipratropium bromide [11,21]	**Dose:** 1 – 2 sprays of 21ug/spray every four hours as needed **Maximum dose:** 168ug/day [21]
	Botulinum Toxin A and B (Xeomin/Botox) [22,21]	**consult with specialist**
Nausea and vomiting	Nausea and/or vomiting is a well-known adverse effect of dopaminergic drug treatment. [12] Other causes include gastroparesis. [23]	
	Domperidone [11,14]	**Dosing:** 10mg TID before meals or PD medications (if nausea is due to these medications) up to a maximum of 30mg per day Watch for QT prolongation especially with drugs with similar concern

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Bladder dysfunction	Bladder dysfunction presents as urinary urgency, frequency and nocturia and difficulty with urination in persons with Parkinson's disease. [5,12] Nonpharmacologic options for the treatment of bladder dysfunction include: - Easing access to bathrooms through use of assistive devices, ensuring pathway to bathroom is clear of obstacles, optimizing control of motor symptoms of Parkinson's disease [5] - Timed voiding - Avoidance of fluids after 6pm, avoidance of coffee [5] - Sleeping with head tilted up [5]	
	Tolterodine (Detrol LA®) [14]	**Dose:** 4mg QHS Adjust dosing for declining renal function Watch for anticholinergic adverse effects
	Solifenacin (Vesicare®) [14]	**Dose:** 5mg QHS Watch for anticholinergic adverse effects
	Fesoterodine (Toviaz) [14]	**Dose:** 4-8mg QHS Watch for anticholinergic adverse effects
	Darifenacin (Enablex®) [14]	**Dose:** 7.5mg QHS Watch for anticholinergic adverse effects
	Mirabegron (Myrbetriq®) [14]	**Dose:** 25mg once daily
	Trospium Chloride (Trosec®) [14]	**Dose:** 20mg QHS Watch for anticholinergic adverse effects
	Desmopressin (Nocdurna®)	**Dose:** 25-50mg SL QHS Monitor serum sodium within 4-8 days and in 1 month to prevent hyponatremia. Not recommended if CrCL< 50 mL/min or history of SIADH or in frail elderly or patients with cardiac insufficiency

Non-motor symptom	Generic name (brand name)	Initial dose and comment
PD dementia (↑ with age and PD duration)	Cognitive impairment and dementia are common occurrences in persons with Parkinson's disease. Dementia presents in 30 – 60% of patients with Parkinson's disease. [5] Cholinesterase inhibitors may improve apathy, behavioural disturbances, and hallucinations. Cholinesterase inhibitors are not recommended if person presents with first or second degree heart block, syncope, or significant bradycardia. Cholinesterase inhibitors must be titrated slowly. Requires slow dose titration. There is less evidence to support the use of galantamine and memantine, a NMDA antagonist, for the treatment of Parkinson's disease dementia.	
	Rivastigmine (Exelon®) oral and patch [11,14]	**Initial dose:** 1.5mg BID with food **Usual/maximum dose:** 6mg BID **Patch:** 4.6-9.5mg patch once daily Give in the morning if patient experiences vivid dreams. Monitor for gastrointestinal adverse effects, bradycardia, syncope
	Donepezil (Aricept®) [11,14]	2.5-5 mg once daily with food. **Usual and maximum dose:** 10mg once daily Give in the morning if patient experiences vivid dreams. Monitor for gastrointestinal adverse effects, bradycardia, syncope
	Galantamine (Reminyl®) [11,14]	**Initial dose Immediate release (IR):** 4mg BID with food **Extended release (ER):** 8mg once daily with food **Usual dose: IR:** 8mg BID; ER: 16mg once daily **Maximum dose IR:** 12mg BID; 24mg once daily Give in the morning if patient experiences vivid dreams. Monitor for gastrointestinal adverse effects, bradycardia, syncope
	Memantine (Ebixa®) [14]	Start with 5mg every morning, titrate to 10mg BID. Maximum dose is limited to 10mg/day if severe renal impairment

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Visual Hallucinations	Psychotic symptoms are common in Parkinson's disease. Hallucinations are common in persons with Parkinson's disease, presenting in 15 – 50% of patients. [5,12] Not all hallucinations require pharmacological treatment, especially if they do not invoke fear or harmful behaviour. [5] Prior to initiating drug treatment for hallucinations, rule out other medical causes of delirium, taper or stop sedative, anxiolytic, and anticholinergic therapy, reduce the dose of or discontinue dopaminergic medications according to the following order to minimize risk of worsening PD: anticholinergics, amantadine, MAO-B inhibitor, dopamine agonist, entacapone, levodopa.[3,5,12] Do not discontinue these medications abruptly, ensure they are tapered off safely. Antipsychotic agents decrease hallucination from excessive dopamine. However, avoid all antipsychotics, but quetiapine and clozapine (and pimavanserin, although it is not currently available in Canada), as they can worsen the control of Parkinson disease symptoms. It is advisable to use lowest dose to avoid sedation and low blood pressure. Antipsychotics increase the risk of mortality in persons with dementia and must be used judiciously. [5]	
	Clozapine (Clozaril®) [14]	**Initial dose:** 6.25mg QHS. May be titrated to effective or maximum dose by 6.25 – 12.5mg every week. **Maximum dose:** 50mg/day. Requires regular blood monitoring due to life-threatening agranulocytosis. Register with CLOZARIL registry.
	Quetiapine (Seroquel®) [11,14]	**Initial dose:** 12.5-25mg QHS **Maximum dose:** 300mg QHS
Apathy	A decrease in motivation and resulting goal directed behaviours commonly presents in persons with Parkinson's disease. [5,24] In early disease, it may be present is 20 – 36% but the prevalence increases 60% in patients with dementia. [24]	
	Rivastigmine	**Patch:** 9.5mg/day [24] Give in the morning if patient experiences vivid dreams. Monitor for gastrointestinal adverse effects, bradycardia, syncope

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Apathy	Pramipexole	For dosing information, see section of Dopamine Agonists
	Rotigotine	For dosing information, see section of Dopamine Agonists
	Methylphenidate	Initiate treatment at the lowest dosage possible and titrate based on individual response
Sexual Dysfunction	Sexual dysfunction can present in both men and women with Parkinson's disease. [3,5] Other causes for erectile dysfunction in men should be investigated. These include mood dysfunction, motor disability and adverse effects of commonly used medications such as beta blockers, alpha adrenergic agents, thiazide diuretics and antidepressants. [5,12,20,24,25] Adding or adjusting dopaminergic drug treatment may be helpful but may also elicit hypersexuality. [5] Nonpharmacologic therapy includes vacuum pump devices.	
	Sildenafil (Viagra®) [5]	**Dose:** 50 – 100mg 1 hour before sex Monitor for hypotension and dizziness
	Vardenafil (Levitra®) [5]	**Dose:** 10mg 1 hour before sex Monitor for hypotension and dizziness
	Tadalafil (Cialis®) [5]	**Dose:** 10mg 30 minutes to 1 hour before sex Monitor for hypotension and dizziness
	Apomorphine sublingual [5,26]	**Dose:** 2 – 4 mg 30 minutes before sex
	Alprostadil Injections: (Caverject) Intrauretral: (Muse) [14]	**Initial dose for injections:** 2.5mcg Dosing must be initiated and titrated in a healthcare setting **Intraurethral:** 125 – 250mcg

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Orthostatic Hypotension	Although up to 50% of persons with Parkinson's disease experience orthostatic drop in their systolic and diastolic blood pressure of ≥20 and ≥10 mmHg, respectively, within 3 min of standing up, only 16% are symptomatic. [20,25] Non-symptomatic orthostatic hypotension does not require treatment with pharmacologic agents. Treatment should be initiated if patients present with dizziness, lightheadedness, blurry vision, or syncope related to orthostatic hypotension. Attempt the following before initiating treatment: - Reassess the need for concurrent antihypertensive agents, drugs that cause vasodilation (for e.g. phosphodiesterase inhibitors), and block norepinephrine release (for e.g. tricyclic antidepressants) [25] - Advise patients to avoid large meals if it occurs after a meal[5] - Advise patients to avoid alcohol [5] - Advise patients to increase salt and fluid intake to 2 – 2.5L/day [5,25] - Advise patients to avoid straining stool [25] - Advise patient to elevate top of the bed (head-up tilt of bed) [5] - Advise patient to wear elastic stockings [5,25] - Advise patients change position carefully and gradually, especially when moving from sleeping to sitting or sitting to standing positions [25]	
	Pyridostigmine Bromide (Mestinon®) [26]	**Dose:** 30mg BID - 60mg TID May increase drooling and urinary frequency and diarrhea
	Midodrine [12,25]	**Initial Dose:** 2.5mg BID **Maximum dose:** 10mg TID Last dose should be given no later than mid-afternoon to prevent supine hypertension at night.
	Fludocortisone [5,25]	**Dose:** 0.5-0.1mg daily **Maximum dose:** 0.2mg/day Monitor for pedal edema and hypokalemia
	Domperidone [14]	10mg TID

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Orthostatic Hypotension	**Desmopression** [12]	**Dose for intranasal administration:** 5-40mg QHS **Dose for sublingual administration:** 25-50mg QHS Monitor serum sodium within 4-8 days and in 1 month to prevent hyponatremia. Not recommended if CrCL< 50 mL/min or history of SIADH or cardiac insufficiency. High risk of supine hypertension at doses of 100-400mg QHS, therefore, not a drug of choice.
Insomnia	Persons with Parkinson's disease experience several different types of sleep disorders including sleep disturbances and insomnia, excessive daytime sleepiness, REM behaviour sleep disorder, and restless legs syndrome. [5,12,20]. The etiology is multifactorial: pain, tremor, stiffness, medication side effects, anxiety, nocturia, among others. A thorough assessment of sleep complaints must be conducted to address underlying treatable contributors before initiating pharmacological treatment; for e.g. optimization of night time dopaminergic treatment must be undertaken to ensure motor symptoms of Parkinson's disease are well controlled. [5,12,20,27] Additionally, a review of medications that may be contributing to sleep disorders must be undertaken.[5] Non-pharmacologic treatments includes: - Ensuring patients follow a good sleep hygiene, including a regular pattern of sleep, restricting daytime napping, and avoiding staying in bed if not asleep [5,12,20,27,28] - Advising patients to avoid caffeine in the evening [5] - Advising patients to increase daytime activity and exercise as directed by a healthcare professional [5,27,28] - Cognitive behaviour therapy [27]	
	Doxepin (Silenor®) [5,14,20,27,28]	**Initial dose:** 3mg QHS **Maximum dose:** 10 mg QHS Dose within 30 minutes of bedtime. Potential for anticholinergic adverse effects
	Melatonin [5,20,27]	**Dose:** 3 – 15mg QHS **Dose:** 5-10mg timed release formulation at bedtime
	Trazodone [5,12,14]	**Dose:** 25-50mg QHS Trazodone can increase the risk of hypotension and falls in the older adult

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Insomnia	Mirtazipine [12,14]	**Dose:** 7.5-15mg QHS
	Zopiclone (Imovane®) [14]	**Initial dose:** 3.75mg QHS **Maximum dose:** 5mg QHS Not a drug of choice as it increases the risk of falls, fractures and cognitive impairment.
Excessive Daytime Sleepiness	Methylphenidate (Biphentin®, Concerta®, Ritalin®) [5,12,14,27,28]	Initiate treatment at the lowest dosage possible and titrate based on individual response (1mg/kg TID for 3 months)
	Modafinil (Alertec®) [5,12,14,27,28]	**Initial Dose:** 100-200mg every morning Trial of caffeine 200mg BID and rule out sleep apnea first Monitor for increase in blood pressure, nervousness, anxiety and headaches.
REM Behaviour Sleep Disorder	Clonazepam (Rivotril®) [3,5,11,12,28]	0.25 – 1mg QHS More effective than melatonin but higher adverse effect profile
	Melatonin [3, 5,11,12]	**Dose:** 3-15mg QHS **Dose:** 5-10mg timed release formulation at bedtime
Restless Leg Syndrome (RLS)	Iron deficiency (with low ferritin) may cause RLS [27,28,29]	**Dose:** Ferrous sulphase 325mg with vitamin C BID If serum ferritin <50 – 75ug/ml, initiate iron supplementation
	Levodopa	**Dose:** 100 – 200mg daily
	Pramipexole (Mirapex®) [5,15,29]	**Dose:** 0.125-0.5mg QHS
	Ropinirole [29]	**Dose:** 0.25mg once daily
	Rotigotine [29]	**Dose:** 1mg patch once daily
	Pregabalin (Lyrica®) [28,29]	Start with 50mg QHS and slowly titrate up to 150mg per day (two to three divided doses)

Non-motor symptom	Generic name (brand name)	Initial dose and comment
Restless Leg Syndrome (RLS)	**Gabapentin** (Neurontin®) [14,28,29]	**Initial dose:** 300mg QHS **Usual dose:** 900 – 1200mg/day in divided doses (TID) Adjust dosing for declining renal function Titrate dosing to effect; taper when discontinuing Watch for respiratory depression, sedation, dizziness, fatigue and edema (legs, ankle or feet), weight gain

Drug-induced Parkinson's disease

Several medications may also cause Parkinsonian symptoms, worsen the control of PD or un-mask PD. Drugs or pharmacological classes commonly associated with drug-induced PD include first- and second- generation antipsychotics, centrally acting dopamine-blocking antiemetics, some cardiovascular medications, among others. [30,31,32] In some individuals, discontinuation of the offending agent can result in a resolution of parkinsonian symptoms, though this may take several months. [30,31]

Medications that may cause drug-induced parkinsonism (DIP) or worsen symptoms of Parkinson's disease *[30,31]*

Class of Medications	Medications to Avoid (higher risk of DIP)
Antipsychotics	**First-generation Antipsychotics** (e.g. chlorpromazine, haloperidol) **Second-generation Antipsychotics** (e.g. risperidone, olanzapine, ziprasidone, aripiprazole)
Nausea Drugs/GI Motility Agents	Prochlorperazine, metoclopramide, promethazine
Calcium Channel Blockers	Flunarizine
Dopamine Depleters	Tetrabenazine

Glossary

Dyskinesia: Involuntary or unusual movements, such as jerking, twitches or spasms. They can affect any part of the body. The strength of dyskinesias can vary from mild to severe. Dyskinesia happens because of the combination of the condition and Parkinson's medication. It is most common in people who have been taking levodopa for many years. The prescription often has to be adjusted to find a balance between enough medication to control the symptoms, and a dose that does not bring on too much dyskinesia.

"On/Off": Describes changes in the ability to move, which happens in some people with long-standing Parkinson's who take levodopa. In the 'on' state, the person can move, while in the 'off' state, they can stop moving altogether. People can switch form one state to the other in minutes or even seconds.

"Wearing-off": An effect experienced by many people who have been taking Parkinson's drugs for some time. The dose does not work for as long as it used to and the beneficial effects wear off before it is time to take the next dose.

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PD NMS QUESTIONNAIRE

Name: ..... Date: ..... Age: .....

Male ☐ Female ☐

NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it **during the past month.** The doctor or nurse may ask you some questions to help decide. If you have **not** experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

	Yes	No
1. Dribbling of saliva during the daytime	☐	☐
2. Loss or change in your ability to taste or smell	☐	☐
3. Difficulty swallowing food or drink or problems with choking	☐	☐
4. Vomiting or feelings of sickness (nausea)	☐	☐
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☐	☐
6. Bowel (fecal) incontinence	☐	☐
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☐	☐
8. A sense of urgency to pass urine makes you rush to the toilet	☐	☐
9. Getting up regularly at night to pass urine	☐	☐
10. Unexplained pains (not due to known conditions such as arthritis)	☐	☐
11. Unexplained change in weight (not due to change in diet)	☐	☐
12. Problems remembering things that have happened recently or forgetting to do things	☐	☐
13. Loss of interest in what is happening around you or doing things	☐	☐
14. Seeing or hearing things that you know or are told are not there	☐	☐
15. Difficulty concentrating or staying focussed	☐	☐
16. Feeling sad, 'low' or 'blue'	☐	☐
17. Feeling anxious, frightened or panicky	☐	☐
18. Feeling less interested in sex or more interested in sex	☐	☐
19. Finding it difficult to have sex when you try	☐	☐
20. Feeling light headed, dizzy or weak standing from sitting or lying	☐	☐
21. Falling	☐	☐
22. Finding it difficult to stay awake during activities such as working, driving or eating	☐	☐
23. Difficulty getting to sleep at night or staying asleep at night	☐	☐
24. Intense, vivid dreams or frightening dreams	☐	☐
25. Talking or moving about in your sleep as if you are 'acting' out a dream	☐	☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☐	☐
27. Swelling of your legs	☐	☐
28. Excessive sweating	☐	☐
29. Double vision	☐	☐
30. Believing things are happening to you that other people say are not true	☐	☐

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998.

Developed and validated by the International PD Non Motor Group
For information contact: susanne.tluk@uhl.nhs.uk or alison.forbes@uhl.nhs.uk

To download and print additional full size copies of this tool, visit www.parkinson.ca.

PARKINSON DAILY DIARY

http://www.cmdg.org/MDC_tools/PDDIARY/pddiary.htm

Name: _____

Date: _____

Instructions: This is a tool to track response to medication and will be used to adjust the doses and timing of medications. Please place only one checkmark under each time of day column in the row that best describes the patient's motor state over the 1-hour period before the time indicated (i.e., in the 7:00 a.m. column indicate the average motor state from 6:00 to 7:00 a.m. or if asleep check only the asleep row.

Motor State – Time of Day	"ON" with Dyskinesia Too Much Movement	"ON" Normal Movement	"OFF" Too stiff and slow	Asleep	PD Medication Time
6:00 a.m.					
7:00 a.m.					
8:00 a.m.					
9:00 a.m.					
10:00 a.m.					
11:00 a.m.					
Noon					
1:00 p.m.					
2:00 p.m.					
3:00 p.m.					
4:00 p.m.					
5:00 p.m.					
6:00 p.m.					
7:00 p.m.					
8:00 p.m.					
9:00 p.m.					
10:00 a.m.					
11:00 a.m.					
Midnight					

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