Parkinson's Disease Dx and Early Management
Prepared Dec 2022 by Doug Hobson
Douglas.Hobson@umanitoba.ca – I am available to answer questions.

Suggested references:

1) MDS Clinical Diagnostic Criteria for Parkinson's Disease
   Postuma et al, Movement Disorders, Vol. 30, No. 12, 2015
2) International Parkinson and Movement Disorder Society Evidence-Based MedicineReview: Update on Treatment for the Motor Symptoms of Parkinson's Disease
   Susan Fox et al, Movement Disorders Aug 33(8):1248-66 2018
3) Canadian Guideline for Parkinson Disease, 2nd Edition, Parkinson Canada
4) Factors impacting on Quality of Life in Parkinson's Diseaase: Results from an International Survey, The Global Parkinson's Diseasee Survey Steering Committee, Movement Disorders Jan 2002
5) Educational Needs and Considerations for a Visual Educational Tool to Discuss Parkinson's Disease.
   Sean Udow et al Movement Disorders Clinical Practice, 5(1):66-74, 2017
6) Palliative stage Parkinson's Disease: Patient's and family experiences of health care services Palliative Medicine 23. 120-25, 2009
7) Nonotor Fluctuations in Parkinson's Disease. Frequent and disabling
   Witjas et al, Neurology 59:408-13, 2002
8) The Queensland Parkinson's Project: An Overview of 20 Years of Mortality from Parkinson's Disease
   Poorvliet et al Journal of Movement Disorders 2020;14(1):34-41.

Suggested internet resources: www.parkinson.ca

Parkinson's disease timeline:
The average life span of Parkinson's disease after dx , based on motor signs is 20 years. It is now known that a collection of "Premotor" features can develop as far back as 20 years earlier, including; constipation, loss of sense of smell, sleep disorders, anxiety and depression, fatigue, and weight change.

Pathophysiology:

The abnormal protein within neuronal Lewy Bodies, is called alpha synuclein. In 2003 a Dr Braak studied 110 brains and determined there was a slow pattern of spread of this protein. The initial changes occur in the olfactory nerve and the area of the lower brainstem that regulates bowel motility (Dorsal Vagal Nucleus in medulla). We now know most PD cases have loss of sense of smell and constipation for years prior to their diagnosis.

The pathology then over time spreads to affect the higher brain stem causing the typical Parkinson features, followed by involvement of even more widespread regions of the brain leading to memory changes.

We know ~ 16% of cases of PD have a family Hx confirming a genetic contribution on top of environments causes. Many specific genes have been identified but thus far these do not lead to differing treatment. They can sometimes help determine prognosis.

Initial Diagnostic considerations:

When you suspect a Dx of PD, management starts with that 1st appointment.

Keep in mind the 3 most common tremor types are medication induced, Essential Tremor and PD. Drug induced tremors are expected to be bilateral and tend to come out with aging even on doses of medications that did not cause tremor at a younger age. Tremor inducing medications are many but include Dopamine blocking agents (including typical and atypical neuroleptics), Anticonvulsants (VPA), Ca Channel Blockers, Antinauseants (Prochlorperazine, Metochlopramide), Antidepressants (SSRIs, SNRIs, Lithium).

Essential tremor by definition has to be there for > 3 years for accurate Dx. It is expected to be bilateral (sometimes asymmetric), flexion / extension and with a positive family Hx 70% of the time. It is an action tremor that improves at rest. PD tremor is a tremor at rest but can be tricky as if a posture is maintained then it can rest and become evident again, such as when holding a phone to your ear or holding a book or newspaper.

Watch the patient walk in from the waiting room. General slowness of movement, asymmetric arm swing, shuffling gait, stooped posture are the early features to look for.

Keep in mind Parkinsonism is not equal to Parkinson's disease. Other conditions besides Parkinson's disease can cause a person to look Parkinsonian, or have "Parkinsonism".

Side effects of certain medications is a common explanation. Other neurodegenerative diseases which referred to as "Atypical Parkinsonism" or "Parkinson plus" syndromes and tend to progress more quickly and respond less well to medications. Brain damage from infections, head trauma, or stroke can also mimic Parkinson's but tend not to respond to medications.

The main atypical subtypes include;

PSP – Progressive Supranuclear palsy - Recognized by early falls, neck rigidity, a startled facial expression, poor speed and range of eye movements.

DLB - Dementia with Lewy bodies is a parkinsonism associated with early dementia, fluctuating degrees of confusion and hallucinations

MSA - Multiple system atrophy is a parkinsonism associated with failure of the automatic bodily functions (Autonomic) including blood pressure control, bladder and bowel and sexual function as well as strained breathing.

CBD – Cortical basal degeneration (or syndrome) is a parkinsonism associated with mainly one sided symptoms, associated with higher level dysfunction due to an inability to figure out how to use the limbs involved in addition to the parkinsonism. Memory loss is also common. All of these have a more severe prognosis due to their more rapid progression and poor medication response.

Early features:

Although the patient most frequently notices the tremor that leads to the diagnosis, their family or doctor are commonly the ones that notice the other features. Friends will notice the tremor, loss of facial expression, the tendency to appear depressed (even when not), more rapid aging, quieter voice, slow walking and loss of clarity of writing. The patient may note the tremor, shoulder aching, loss of dexterity, fatigue, a long standing problem with constipation, loss of sense of smell, need to repeat to be heard, change in writing size (micrographia) and drooling especially at night. The average age of onset is now 59 years of age.

Making the clinical Diagnosis:

There are no blood tests or routine xrays that can confirm Parkinson's disease. This is a diagnosis based on clinical features. There must be slowness of movement along with either tremor at rest or muscular stiffness or both. Characteristically these features start on 1 side of the body and on average take 2 years to start to affect the other side. Additional clues on exam will be a stooped posture, shuffling gait with reduced stride length, reduced arm swing, loss of facial expression, quieter voice, along with the history of loss of sense of smell and constipation.

The key feature is slowness of movement specifically "Bradykinesia", which is associated with reduction of the speed and rhythm with repeated movements called **decrement**. The patient will require multiple steps to make a turn ("turning en bloc") and with progression gait initiation will become difficult. Balance gradually becomes impaired and the ability to maintain an upright posture becomes abnormal due to a loss of knowing where the center of gravity is.

Revealing the Diagnosis:

Evidence suggests the patient experience, during the appointment when the diagnosis is given to them , can affect their QOL for years after. Letting them know the diagnosis needs to go well. Honesty, compassion (even with hand holding) improves the experience. Take time.

If there is uncertainty regarding the Dx then refer to a specialty clinic. Unless the situation has advanced to the stage that the patient would be put at risk if medication was not started, hold off on treatment until the diagnosis can be confirmed.

One way the conversation could go:

"I am concerned you may have Parkinson's disease. This is a condition that can be difficult to Dx early on. It cannot be confirmed by blood tests or imaging. It is diagnosed based on findings in your history and on exam. We look for slowness in addition to stiffness and or tremor when relaxed.

There is no need to start medication as soon as the diagnosis is made but we also do not want to delay them if your work or QOL is being affected. If the pattern of presentation is one sided tremor, then this corelates with a slower progression and usually a good response to medication. I will be able to provide you with a more accurate prognosis over time."

Using pictures to help with the explanation of the condition is useful. Providing a disease specific online resource such as www.Parkinson.ca is recommended. Letting them know of a free handbook to assist them in management and understanding the condition is beneficial - "Every Victory Counts" is available at www.Parkinson.ca).

See them again soon to allow them to clarify questions they will come up with.

Recommendations re management:

Key aspects that require early attention and ongoing monitoring:

Exercise – You need to make an "athlete out of them". The goal is 3 hours of cardiovascular fitness (some huffing and puffing) per week.

Hydration – PD patients lose their sense of thirst. They become dehydrated easily. This will aggravate fatigue, hypotension, constipation, balance and fall risk.

Constipation Rx – Exercise, fruit and fiber and hydration as a routine with addition of an osmotic laxative or bowel stimulant when needed. GI referral should be considered when this is refractory to routine Rx.

Healthy diet and lifestyle with attention to good sleep hygiene and well rounded diet with well timed rest periods.

Life planning advise: Counselling may be required for advice as to who and when to reveal the Dx to, financial planning, options re disability plans, driving safety issues, and advanced life planning (health proxy, will, health care directive. Family / care providers should be encouraged to attend all appointments. This illness affects the family!

Driving: MPI needs to be informed of this illness as with the combination of a reduced reaction time and progressing cognitive slowing, the risk of an accident increases. Not infrequently periodic road tests will be recommended to ensure safety on the road.

Movement Disorder Clinic involvement:

Canadian guidelines recommend this condition be cared for in an interdisciplinary specialty clinic. In Manitoba, the Deer Lodge Movement Disorder Clinic provides this model of specialty care for Parkinson's disease.

Continuing regular follow up with the primary care physician is needed. This should be a team approach. The patient and care providers need the primary physician's skills regarding ongoing point of contact to coordinate their overall care including co-morbidities. They can take advantage involvement with the MDC by accessing the clinic nurse coordinator and the specialty services within the clinic including PT, OT, Speech and Swallowing therapist, Social Worker, Dietician and the Deep Brain Stimulation (DBS) clinician along with other advanced therapy expertise.

Early Phase PD

Early on the affected individual remains independent and still has good motor and cognitive abilities and remains fully engaged with their social and work life. At this stage though, there are problems that need attention. 40% have pain. 50% have depression or apathy, 50% have anxiety, 70 have sleep disorders. Self esteem, financial well being, and their employment are put at risk. Support systems may be strained. Their family dynamics can be affected.

Non motor symptoms:

The main deficit is an inability to produce normal amounts of dopamine. This mainly affects movement ability but can also lead to cognitive and emotional changes as well as a reduction in motivation. Norepinephrine and serotonin production is also impaired affecting mood, sleep, appetite, sexual desire, pain sensitivity, and motivation.

The collection of non-motor symptoms are frequently present and tend to have a greater impact on disability and quality of life than the motor symptoms.

Sleep

Avoid stimulants particularly later in the day.

The most common reason for sleep fragmentation is nocturia. This is something the primary care physician can work up to rule out causes unrelated to PD and treat accordingly. Urodynamic testing / Urology consultation to guide proper pharmaceutical Rx.

PD rigidity through the night with advancing disease may require use of levodopa through the night or use of the Rotigotine patch.

Insomnia related to anxiety / restless thinking may need focussed Rx such as an SSRI. HS Quetiapine can be considered. Doxepin or trazadone can be useful.

A formal Sleep Study is often needed to diagnose sleep apnea or RLS with Periodic Leg Movements of Sleep (PLMS), and can assist in explaining daytime somnolence and allow specific Rx to be introduced.

REM sleep disorder wherein patients retain the ability to move during their dreams can cause self injury and injury to the bed partner. This often responds well to Melatonin (5-30 mg HS) at bedtime. Clonazepam although effective is poorly tolerated in this population due to cognitive and balance side effects. Removing potentially dangerous objects from around the bed and placing a foam mat on the ground can increase patient safety.

Orthostatic Hypotension

This doesn't always cause dizziness when standing, but often does. It can be the cause of increased falling, poor concentration, fatigue, loss of motivation, nausea, and a posterior head and neck ache when upright (coat hanger headache).

Confirm by checking BP (after 5 minutes lying) then while standing (immediately and at 1 and 3 minutes) BP. Confirm if systolic drops > 20 or diastolic drops by > 10.

Treatment starts with avoiding situation when this will be worse – eg hot environments, hot baths, large meals, standing too long in one place. Rx includes adequate hydration, reducing antihypertensive medications and removing hypotensive meds that may not be absolutely necessary (eg tamulosin). Domperidone 10 mg TID will block the hypotensive effect of Levocarb by blocking the peripheral receptors that trigger vasodilation. (it is a QT prolonger so monitoring with periodic EKG is indicated. Increased salt intake, elevating the head of the bed at night, pressure stockings are non-medication approaches. Fludrocortisone and Midodrine may be needed. Cardiology input can be needed.

Depression and anxiety:

These occur in 30% of cases and can precede the diagnosis. This is managed in the same way as anxiety and depression in cases without Parkinson's. Keep in mind many of the physical features we use to help with the diagnosis of depression will be masked, so a focussed history becomes more important to assist in making a Dx of depression. Consider using a self completed Beck's Depression Scale to assist in the diagnosis.

Selegiline and pramipexole do have some antidepressant and anti-apathy potential.

Fatigue (separate from sleepiness):

Evident in 74 % of my patient's during follow up apts. Fatigue is multifactorial and a systematic approach is needed as many contributing factors can be treated. Think under treated PD, Depression, Sleep disorders, Orthostatic hypotension, and or Boredom. Don't forget side effects of medications and systemic illnesses. Fatigue may end up being idiopathic.

Pain

PD patients have lower pain thresholds than the normal population. Don't blame everything on PD though. PD can cause muscle pain / cramping / dystonia but expect to hear a correlation between the timing of the pain and the timing of their medications. It may be a wearing off symptom and respond to adjustment of the timing of their PD meds.

PD doesn't prevent patients from having other non-related issues causing pain and as such primary care providers are relied on to investigate and treat this.

Hallucinations / Psychosis:

This typically begins as an illusion of presence – getting the feeling someone is behind you. This can progress to delusions and can cause paranoia including about partner infidelity. True hallucinations can follow. As Parkinson's will be worsened by typical neuroleptics (they block dopamine), management involves reducing causative agents if possible or using quetiapine or clozapine as they won't worsen Parkinson's. All PD medications other than levodopa are more likely to have this side effect in comparison to levodopa relative to their efficacy.

Parkinson's Medication Management:

There are no medications that halt or slow the progression of Parkinson's disease.

All medications for Parkinson's are used in attempt to improve the symptoms. There is no proven need to start them as soon as a diagnosis is made. They are introduced to try to maintain function and quality of life – both at work and home.

The aim is to resolve the dopamine deficiency state. This can be done best with dopamine replacement using regular release Levodopa / Carbidopa (Levocarb / Sinemet / Prolopa).

There is no hurry – go slow with the introduction. I start **levodopa carbidopa** at ½ a 100/25 tab PC AM and every 3-4 days add another ½ tab spreading gradually out to TID PC, then working up to 1 tab TID before review. Some will need up to 600 mg / day to see an effect. If doses higher than that seem needed, this should trigger a referral.

The **levodopa – Bensarizide** product (prolopa) can be better tolerated than levodopa carbidopa in some cases. It comes in capsule form.

These medications do not take long to work once on an effective dose. The goal is not full control of all signs, just functional improvement.

If nausea is a limiting side effect use domperidone 10 mg TID.

A **250/25 tab** can be used instead of 2.5 tabs of the 100/25 pills to reduce the total number of medications. Also using ½ a 250/25 gets a 125 mg dose and this allows for an ability to titrate

increasing doses more slowly. An example would be instead of jumping from a 1 x 100/25 tab to 1 ½ tabs (100 to 150 mg of levodopa is a 50 % increase) one can use this to increase by only 25%. Only a total of 75 mg of carbidopa is needed when using levodopa.

Long acting **Sinemet CR** is erratically absorbed so is often only used as an HS Rx.

Changing the chemical imbalance in favour of Dopamine by blocking acetylcholine with "**anticholinergics** (eg. Trihexyphenidyl) is an option but the medications that can have this effect are often poorly tolerated especially in the elderly and need to be used cautiously if at all. Beware their constipating and cognitive effects.

Amantadine acts to block acetylcholine as well, but also seems to have other effects on Dopamine receptors making it useful to treat Parkinson symptoms as well as the excessive movements (Dyskinesia).

Agonists do still have a role in younger patient's when fluctuations become problematic but the frequent and serios side effect potentials often make these a poor choice. Impulse control disorders and somnolence to the point of falling asleep at the wheel remain major considerations and points of discussion when considering these.

Rotigotine is a 24 hour dopamine agonist skin patch that is now more commonly considered especially pending DBS or when over night control is needed.

Disease progression:

Once diagnosed, this neurodegenerative disease continues to slowly worsen. Fluctuations become increasingly prominent after this stage requiring more medications and more frequent dosing. The goal of medications is to obtain a blood level of dopamine receptor stimulation within the "therapeutic window". On average the first 3 years is spent in a honeymoon period when the medications provide an even response all day long. Then fluctuations in response begin.

As Parkinson's disease progresses, the therapeutic window narrows. Too high a dose can trigger side effects including excessive movements and confusion. Too low a dose will not achieve adequate symptom control. This causes a greater reliance on medications to replace the dopamine that the Parkinson brain becomes less and less able to provide. Fluctuations in the blood level of medications result in fluctuations of function. Patients are referred to as "ON" when the blood level is in the therapeutic window and "OFF" when blood levels drop below the effective dose. Involuntary movements "dyskinesia" can occur if the blood level gets too high. Dyskinesia occurs in 50% of young onset cases within 3 years of onset. These are less common with an older age of onset.

Daily diaries of the timing of fluctuations are often needed to guide medication dose and timing to minimize these problems. With progression consistent timing of doses becomes increasingly

important. There are a variety of medication alarms available. A good internet source is www.epill.com.

Management of fluctuations:

There are medications that block the ability of the body to get rid of dopamine which can also provide beneficial effects on their own (as in the case of Selegiline, Rasagiline) or in combination with levodopa in the case of Entacapone and Safinamide.

Surgical: Deep Brain Stimulation (DBS) involves surgically implanting electrodes into the basal ganglia to alter the firing pattern. DBS starts to become an option during the middle stage (5-8 years). This has been confirmed in multiple trials to be more effective than medications once a patient reaches a stage where medications still work but cannot maintain a stable response through the day. This procedure cannot be done safely on elderly cases with cognitive problems.

Duodopa:

Surgical implantation of a tube into the jejunum through a gastrotomy tube and then infusing levodopa in the form of a gel, from an externally worn pump, is an additional option for cases with problematic fluctuations who are not able to tolerate brain surgery. The cost is $60,000 / year.

Rescue Medications:

Apomorphine, a rapidly acting dopamine agonist is available in a subcutaneous injection form and a sublingual wafer. The expectation is a quick transition to feeling “on” within 10-15 minutes and a duration of benefit for 1-2 hours. Due to the risk of nausea and hypotension co-treatment with domperidone is needed.

Advanced PD

From 8-15 years from diagnosis treatment refractory symptoms become increasingly evident. These can, but do not always include balance problems, worsening speech and swallowing, bowel and bladder dysfunction, sleep disorders, and fatigue. Advanced stages of the disease are associated with more frequent confusion, falls, hallucinations, memory loss and loss of independence requiring increasing input from family and home care. Depending on individual situations personal care home placement may enhance patient safety and reduce social isolation. Consulting a **palliative care team** is appropriate at these stages.

Planning for advances stages of the disease should be done early and communicated with a chosen health proxy.

Conversations regarding **MAID** may be indicated on a case-by-case basis.

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Supportive criteria

(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

☐ 2. Presence of levodopa-induced dyskinesia

☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:

☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)

☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades

☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease

☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y

☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism

☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease

☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia

☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system

☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Red flags

☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset

☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment

☐ 3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y

☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs

☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
   a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
   b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction

☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset

☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y

☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)

☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)

☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

Criteria Application:

1. Does the patient have parkinsonism, as defined by the MDS criteria? If no, *neither* probable PD nor clinically established PD can be diagnosed. *If yes:*	Yes ☐	No ☐
2. Are any absolute exclusion criteria present? If "yes," *neither* probable PD nor clinically established PD can be diagnosed. *If no:*	Yes ☐	No ☐
3. Number of red flags present ____		
4. Number of supportive criteria present ____		
5. Are there at least 2 supportive criteria *and* no red flags? If yes, patient meets criteira for **clinically established PD**. *If no:*	Yes ☐	No ☐
6. Are there more than 2 red flags? If "yes," probable PD *cannot* be diagnosed. *If no:*	Yes ☐	No ☐
7. Is the number of red flags equal to, or less than, the number of supportive criteria? If yes, patient meets criteria for **probable PD**	Yes ☐	No ☐