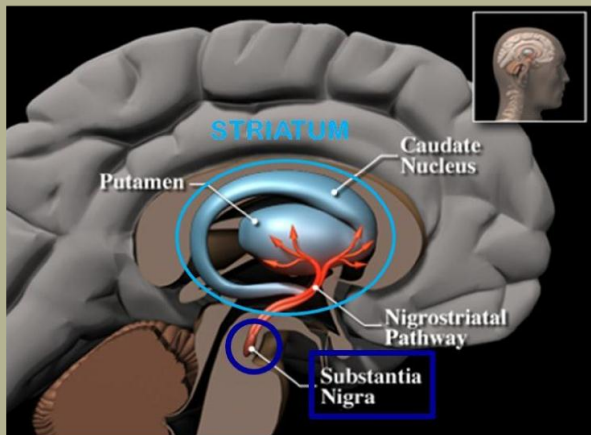
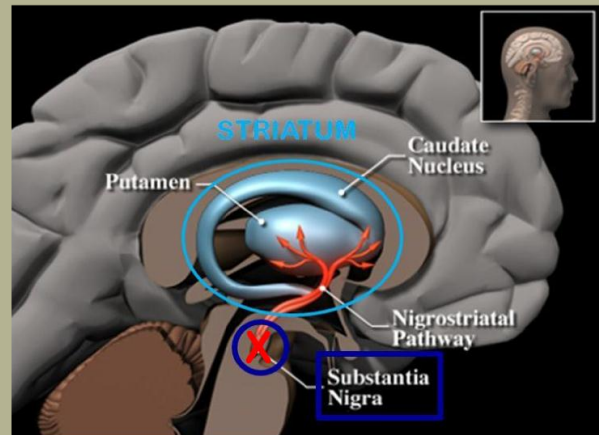


WHAT IS PARKINSON'S DISEASE?

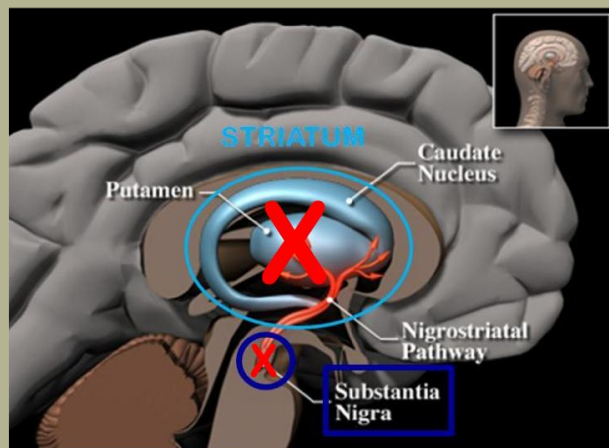
Parkinson's disease (PD) is a progressive condition in which cells in some parts of the brain are lost at a faster rate than normal. The most typical symptoms of PD, and those that are used to make the diagnosis, are problems with movement, such as tremor that occurs at rest, slowness and stiffness, and difficulties with balance. These symptoms are caused by loss of the specialized brain cells that produce the chemical *dopamine*. The figure explains how loss of these cells leads to movement problems in PD.



Cells in the substantia nigra produce **dopamine**, a chemical that is used by the **striatum**. The striatum is a part of the brain that is involved in planning and controlling movements and some aspects of thinking.



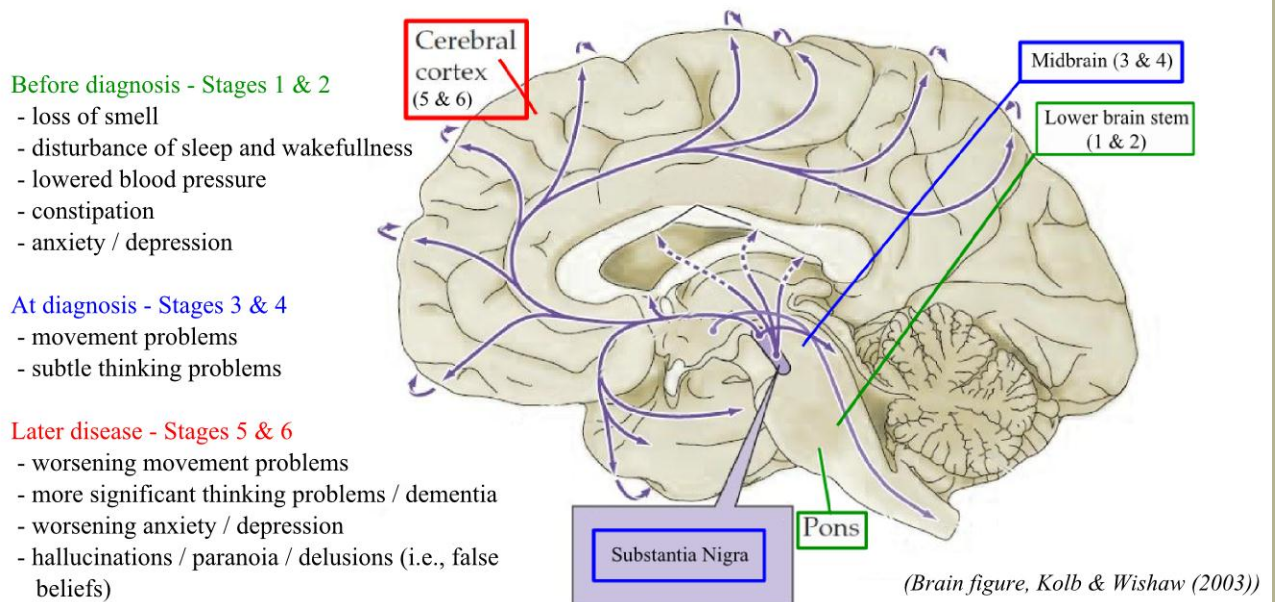
In Parkinson's disease, cells in the *substantia nigra* are lost at a faster rate than usual for the person's age. This causes reduced *dopamine* production.



The striatum doesn't work properly because it receives too little *dopamine*.

Increasingly, we understand that brain regions other than the dopamine-producing cells are also lost at a faster rate than normal in PD, producing symptoms that were not

previously recognized. Some of these symptoms can even appear before the movement problems. Below is a diagram showing a) the different stages of PD, b) the general brain regions that experience premature cell loss at each stage, and c) the broad categories of symptoms that occur at each stage. The diagram depicts the average order in which brain regions are affected as PD progresses and the symptoms that result. Not all patients develop symptoms in this order. The wide variety of symptoms that can occur in PD is presented in detail later in this handout.



PD appears more frequently in people over the age of 50 but on occasion it does develop in younger individuals. Approximately 1-2% of people above age 65 have PD. The cause of PD remains unknown. In about 5% of cases, PD is caused by an abnormality in a single gene and strongly runs in families with many or most family members developing PD symptoms. In the majority of cases, however, having a first degree relative with PD (i.e., mother, father, sister, brother, child) only increases your risk of developing PD slightly (i.e., instead of 1-2% risk, the risk is 3-4%) and therefore other factors, most of which have not yet been identified, are more important than inheritance in determining whether or not you'll develop PD.

WHAT ARE THE SYMPTOMS OF PARKINSON'S DISEASE?

Below are symptoms that can occur in PD. Not all patients experience every symptom.

The problems with movement, termed **motor symptoms**, are the cardinal symptoms in PD, and are required to make the diagnosis. Usually, motor symptoms start on one side of the body and only occur on the other side a couple of years later. The symptoms usually remain more severe on the side of the body that was first affected throughout the disease. Motor symptoms in PD are produced by **too little dopamine** in the *striatum*, as explained above. These symptoms are *significantly* improved by medications that replace dopamine or that act like dopamine in the brain.

Non-motor symptoms are increasingly recognized in PD. Because many of these symptoms also occur in normal aging or in other neurological diseases, it's not possible to make a diagnosis of PD based on these symptoms alone. Most of these non-motor symptoms, listed below, do **not** result from a **lack of dopamine** and therefore do not improve with medications that replace dopamine or that act like dopamine in the brain. Other medications are given to address non-motor symptoms. Unfortunately, therapies available to treat non-motor symptoms are less effective than the medications available to treat the motor symptoms in PD.

MOTOR (MOVEMENT) SYMPTOMS

REST TREMOR

- ✚ especially affects the thumb and index finger, and has a 'pill-rolling' appearance
- ✚ decreases or goes away when muscles are contracted or when actions are performed
- ✚ can appear in hands, legs, head, jaw, chin, voice, or eye-lids

HYPOKINESIA

(decreased number of spontaneous movements) or *akinesia* (lack of spontaneous movements), causing reduced:

- ✚ blinking
- ✚ swallowing (that in turn leads to excess saliva and drooling)
- ✚ facial expressions leading to a blank look (sometimes termed *masked facies*)
- ✚ movement of arms, legs, and body
- ✚ small writing (called *micrographia*)

BRADYKINESIA

(slow movements)

- ✚ loss of balance or difficulty regaining balance (termed *postural instability*) can result

STIFFNESS OR *RIGIDITY* THAT CAUSES:

- + slurred speech, stuttering
- + difficulty chewing and swallowing
- + quiet speech
- + bent/stooped posture
- + involuntary twisting, turning, or abnormal postures (*dystonia*) of arms, legs, hands, feet, neck, face, mouth
 - sometimes these abnormal postures come on only with specific actions such as writing, chewing, speaking, walking
- + balance problems
- + pain

Note: Twenty percent of the population, and hence some patients with PD, have a common condition called essential tremor. Essential tremor is more prominent when muscles are contracted and a posture is assumed (as opposed to the rest tremor of PD). Essential tremor worsens even further when actions, especially those that require fine control such as writing, eating, or threading a needle, are performed. This tremor will not improve with medications given for PD. Therefore patients with PD and essential tremor need to take different sorts of medications to treat their two separate tremors. Sometimes when a tremor does not seem to be responding to PD medication, it is important to evaluate when the tremor is most prominent in case medications for essential tremor are also needed.

NON-MOTOR (NON-MOVEMENT) SYMPTOMS

HYPOSMIA

(decreased sense of smell) or *anosmia* (lack of sense of smell)

AUTONOMIC DYSFUNCTION

(problems with automatic bodily functions)

- + nausea due to slow digestion
- + constipation
- + decreased blood pressure +/- drops in blood pressure with changes in position such as sitting from lying or standing from sitting, termed *orthostatic hypotension*
- + *hyperhidrosis* (excessive sweating), flushing, *sialorrhea* (excessive saliva)
- + runny nose
- + weight gain
- + frequent urination/urination at night
- + erectile dysfunction/decreased vaginal lubrication/impaired orgasm or ejaculation

Note: Autonomic dysfunction is very common and can begin early and worsen with disease progression. For example, occasionally PD patients have low blood pressure when standing and very high blood pressure when lying. This can make it difficult to find the right treatment for blood pressure.

MOOD CHANGES

- + anxiety
- + depression
- + apathy/lack of interest or motivation

COGNITIVE SYMPTOMS

(problems with thinking) (very subtle early and can worsen with disease progression – not occurring in all patients)

- + decreased attention/concentration
- + memory problems
- + problem solving troubles
- + language deficits
- + *dementia* (problems with thinking that cause difficulty or inability to perform activities that were previously performed without difficulty)

Note: Cognitive symptoms don't occur in all patients, or can be very subtle. They tend to worsen with disease progression.

SLEEP AND WAKEFULNESS PROBLEMS

- + excessive daytime sleepiness/fatigue (very common)
- + vivid dreams (early)
- + acting out one's dreams termed *Rapid Eye Movement Behaviour Sleep Disorder (RBD)*
- + insomnia and difficulty maintaining sleep
- + restless legs syndrome

VISION PROBLEMS

- + impaired colour discrimination
- + glaucoma

SKIN PROBLEMS

- + excessively oily skin
- + *seborrheic dermatitis*, an inflammatory skin condition that causes flaky, white to yellowish plaques on oily areas such as the scalp or inside the ear, occurring with or without reddened skin

WHAT ARE THE TREATMENTS FOR PARKINSON'S DISEASE?

Currently, there is no cure for PD and there are no treatments that have been shown to clearly stop or slow the progression of PD. Below is a list of treatments available for motor and non-motor symptoms of PD. The generic name of the medication is presented first and the trade name(s) is/are capitalized and listed second. A brief outline of how the medication works and a list of common side effects is written for some. This list is not comprehensive. Idiosyncratic reactions are always possible so discuss any new symptoms that arise after starting a new medication with a physician.

MEDICATIONS

TREATMENTS FOR MOTOR (MOVEMENT) SYMPTOMS

DOPAMINE PRECURSORS

- + converted to dopamine in the brain
- + the most effective medication to treat movement symptoms in PD
- + the frequency of doses and the amount of medication taken at each dose increase periodically
- + examples:
 - **L-3,4-dihydroxyphenylalanine (L-Dopa)**
 - **carbidopa** slows L-Dopa breakdown, increasing the intensity and duration of L-Dopa action in the brain
 - **benserazide** slows L-Dopa breakdown, increasing the intensity and duration of L-Dopa action in the brain
- + **L-Dopa + carbidopa = levocarb/Sinemet/ Parcopa/Atamet (available as immediate or controlled release tablets)**
 - **L-Dopa + benserazide = prolopa/Prolopa**
- + other symptoms that might be helped
 - some aspects of thinking (attention/concentration, problem solving) although it might slightly worsen others (learning new skills/information)
 - problems with excessive sweating and flushing
- + side effects – discuss these with a physician:
 - nausea – usually goes away but if not can be improved with another medication called **domperidone/Motilium**
 - low blood pressure, especially with changes from lying to sitting or sitting to standing termed *orthostatic hypotension* – causes feeling

lightheaded/ dizzy or passing out, can be improved by
domperidone/Motilium

- increased sleepiness but in some patients can promote wakefulness
- confusion
 - usually only with high doses and at later stages of PD
- *visual hallucinations* - seeing things that aren't truly there
 - usually only with high doses and later stages of PD
- involuntary fidgeting, twisting, flinging, or jerking movements called *dyskinesias*
 - usually only with high doses and at later stages of PD
 - typically when L-Dopa doses are peaking in the blood stream, approximately 1 hour after medication is taken
 - rarely, can occur as medication dosage is increasing and/or decreasing in the blood stream, approximately 30 min after medication is taken and 30 min before the next dose
- rarely, can cause compulsive behaviours such as gambling, shopping, hypersexuality, pre-occupation with video games, collecting items, etc.

DOPAMINE AGONISTS

- ✚ imitates dopamine by binding to dopamine receptors in the brain, mimicking dopamine effects
- ✚ very effective medication to treat movement symptoms but slightly less effective than **levocarb**
- ✚ the amount of medication taken at each dose increases as time from diagnosis of Parkinson's passes
- ✚ other symptoms that might be helped
 - some aspects of thinking (attention/concentration, problem solving) although it might slightly worsen others (learning new skills/information)
 - problems with excessive sweating and flushing
- ✚ examples:
 - **pramipexole/Mirapex**
 - **ropinirole/Requip**
 - **pergolide/Permax**
- ✚ side effects - discuss these with a physician
 - nausea
 - low blood pressure, especially with changes from lying to sitting or sitting to standing termed *orthostatic hypotension* - more significant than with L-Dopa - causes feelings of lightheadedness or faintness, and in some cases patients actually "pass out" or lose consciousness.

- increased sleepiness, more than with L-Dopa - can cause *sleep attacks* (i.e., falling asleep suddenly)
- confusion more significant than with L-Dopa
 - usually only with higher doses and at later stages of PD
- *hallucinations* - seeing things that aren't truly there, more than with L-Dopa
 - usually only with high doses and later stages of PD
- excessive movements called *dyskinesias*, less often and less severe than with L-Dopa
 - usually only with high doses and at later stages of PD
- occasionally (more often than with L-Dopa) can cause compulsive behaviours such as gambling, shopping, hypersexuality, pre-occupation with video games, collecting items, etc.
- swelling of arms and/or legs
- nasal congestion
- can worsen constipation

CATECHOL-O-METHYLTRANSFERASE INHIBITORS

- ✚ slows the break-down of L-Dopa, thereby increasing the effect and duration of action of L-Dopa in the brain
- ✚ examples:
 - **entacapone/Comtan**
 - **tolcapone/Tasmar**
- ✚ side effects:
 - can increase all the side effects described for levocarb/Sinemet/Prolopa
 - diarrhea
 - causes urine and sweat to have an orangey colour

Note: Stalevo is a medication that combines levocarb/Sinemet + entacapone/Comtan in one pill. The medication tolcapone/Tasmar is not used because it has been shown to cause liver damage in some patients.

MONOAMINE OXIDASE TYPE B INHIBITORS (MAOI-B)

- ✚ slows the break-down of L-Dopa, thereby increasing the effect and duration of action of L-Dopa in the brain
- ✚ some suggestion that rasagiline might slightly improve the course of PD
- ✚ examples:
 - **selegiline/Eldepryl or Deprenyl**
 - **rasagiline/Azilect**
- ✚ side effects:
 - can increase all side effects described for levocarb/Sinemet/Prolopa
 - nausea

- insomnia
- If foods/beverages/dietary supplements rich in the amino acid tyramine (e.g. certain cheeses, wines, fermented food & beverages, decongestant medications, some prescription pain medications) are taken along with these medications, an episode in which the heart rate and blood pressure increases dramatically, called a *hypertensive crisis*, could theoretically occur. These reactions have not been observed in the clinical trials for this medication so far. Nonetheless these foods/beverages/dietary supplements should be avoided while taking this medication.

AMANTADINE

- ✚ an antiviral medication that has been shown to slightly improve the symptoms of PD but also has been shown to decrease *dyskinesias* (i.e., excess movements) that are caused by dopamine precursor and dopamine agonist medications.
- ✚ side effects:
 - hallucinations
 - confusion
 - nightmares
 - swelling of the limbs termed *peripheral edema*
 - purplish rash called *livedo reticularis*

ANTICHOLINERGIC MEDICATIONS

- ✚ blocks *acetylcholine* receptors
- ✚ minimally reduces tremor
- ✚ rarely used because very little improvement in symptoms but causes many side effects
- ✚ examples:
 - **trihexyphenidy/Artane**
 - **benztropine/Cogentin**
- ✚ side effects:
 - dry eyes and mouth
 - constipation
 - difficulty with urination
 - confusion
 - hallucinations

TREATMENTS FOR NON-MOTOR SYMPTOM

AUTONOMIC DYSFUNCTION

+ nausea

- **domperidone/Motilium** (also decreases nausea related to dopamine precursor and dopamine agonist medication)

+ constipation

- diet, fibre, **docusate/Colace**, **senna/Senokot**, **lactulose**
- low blood pressure
- increased hydration (at least 8 glasses water per day)
- salt tablets
- **domperidone/Motilium** (also treats orthostatic hypotension caused or worsened by dopamine precursor and dopamine agonist medications)
- **midodrine/Proamatine** (constricts blood vessels to increase blood pressure)
- **fludrocortisone** (increases salt content in blood resulting in water to be drawn into blood vessels)

+ hyperhidrosis (excessive sweating), flushing, sialorrhea (excessive saliva)

- **aluminum chloride hexahydrate/Drysol**
- **glycopyrrolate**
- **botulinum toxin injection/Botox**

+ overactive bladder

- **darifenacin/Enablex**
- **oxybutynin/Ditropan**
- **solifenacin/Vesicare**
- **tolterodine/Detrol**
- **tropium chloride/Trosec**

+ nocturnal polyuria (excessive urination at night)

- **desmopressin spray/DDAVP**

+ urinary retention (difficulty urinating)

- **bethanechol chloride/Duvoid**

+ erectile dysfunction

- **sildenafil/Viagra**

Note: so far there are no treatments proven to improve sexual disturbances related to PD in women

MOOD CHANGES

- ✚ anxiety and depression
 - antidepressant medications (e.g., **citalopram/Celexa**, **venlafaxine/Effexor**)
- ✚ cognitive problems
 - attention/concentration, memory, problem solving
 - dopamine precursors (e.g., **levocarb**) and dopamine agonists (e.g., **pramipexole**) might improve these symptoms somewhat
 - *dementia*
 - **rivastigmine/Exelon**, **donepezil/Aricept**, **galantamine/Reminyl**, **memantine/Ebixa**
 - these medications are only minimally-moderately effective in most patients
- ✚ *hallucinations/paranoid thinking/false beliefs (i.e., delusions)*
 - antipsychotic medication (also known as neuroleptics) (e.g., **clozapine/Clozaril**, **quetiapine/Seroquel**)
 - other antipsychotics that are effective for these symptoms (e.g., **risperidone/Risperdal**, **olanzapine/Zyprexa**) worsen PD movement symptoms and therefore should be avoided if possible.

SLEEP AND WAKEFULNESS PROBLEMS

- ✚ excessive daytime sleepiness/fatigue (very common)
 - **caffeine**
- ✚ acting out one's dreams termed *Rapid Eye Movement Behaviour Sleep Disorder (RBD)*
 - **melatonin**
 - **clonazepam/Rivotril**
- ✚ night-time insomnia
 - **zopiclone/Imovane**
- ✚ restless legs syndrome
 - dopamine agonist (e.g., **pramipexole/Mirapex**) and dopamine precursor (e.g., **levocarb/Sinemet**) medications

VISION PROBLEMS

- ✚ glaucoma
 - eye drops

SKIN PROBLEMS

- ✚ excessively oily skin
 - aluminum chloride hexahydrate/Drysol
 - glycopyrrolate
 - botulinum toxin injection/Botox
- ✚ seborrheic dermatitis
 - botulinum toxin injection/Botox

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is an option for PD patients whose motor symptoms do not respond adequately to medication. It is a surgical procedure in which electrodes are implanted in the brain to provide electrical stimulation to the parts of the brain that control movement. The battery pack or neurostimulator that powers the electrodes is implanted under the skin near the collar bone. It is an effective procedure that can greatly improve symptoms such as tremor, rigidity, slowed movement, and walking problems. Because DBS often leads to less need for medication, patients experience less of the associated side effects. It is an invasive neurosurgical procedure, however, with the usual risks of brain surgery such as bleeding, brain injury, and infection and so should only be considered in select cases.

WHAT TO EXPECT AS PARKINSON'S DISEASE EVOLVES?

Every patient is unique and the number, severity, and rate of progression of Parkinson's-related symptoms differ greatly from one patient to another. PD itself is not a fatal disease, and the average life expectancy for patients with PD is similar to that of people without the disease. In general, younger patients evolve more slowly and have tendency to develop non-motor symptoms, especially thinking problems, much later in the disease course compared to more elderly patients. Many patients, particularly those who do not experience the more troublesome non-motor symptoms, can continue to work and function almost normally for years with treatment.

Penny A. MacDonald, MD, PhD, FRCP(C)

