Parkinson Primer

"pearls" to help health care professionals provide better care for people with Parkinson disease

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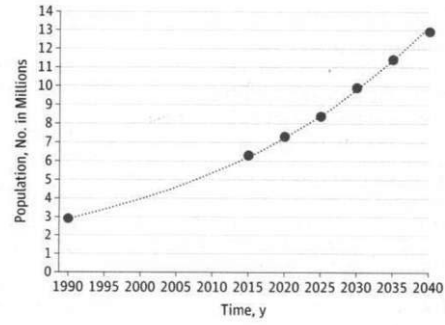
Why be familiar with Parkinson disease?

- It is a very common disorder
- It is a complex but very treatable disorder

"Parkinson disease is a condition where the physician can make a huge difference in the life of the patient. Although not all symptoms can be completely controlled, optimum treatment can keep patients in the mainstream of life."

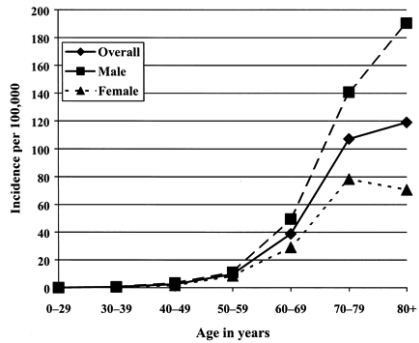
quote from Dr. Eric Ahlskog - Mayo Clinic

Figure. Estimated and Projected Number of Individuals With Parkinson Disease, 1990-2040



Sources: Global Burden of Disease Study (1990 and 2015) and projections based on published[2] and public[3] sources.

Epidemiology of Parkinson disease



- PD occurs world-wide affecting all races and ethnic groups
- The prevalence increases with age, but is most often initially diagnosed in persons who are in their 50s or 60s
- ~95% of cases are sporadic without a strong family history
- Men are affected somewhat more often than women
- PD affects approximately 2% of the US population by age 70

DIAGNOSING PARKINSON DISEASE

Parkinson disease is a very heterogeneous condition, and although the diagnosis might seem obvious in some cases, it can be challenging and subject to error in others.

Diagnosing Parkinson disease

- **The diagnosis is "clinical":**

  (there is no definitive brain imaging study or laboratory test)

Diagnosis relies on

- Taking a complete history
- Carefully examining the patient
- Considering the differential diagnosis

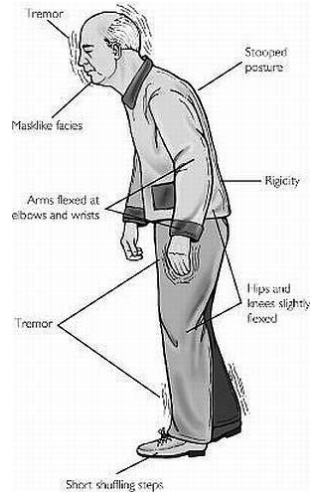
Caveat:

There are other conditions that can mimic Parkinson disease. Even in cases that initially seem "typical", the diagnosis may need to be revised over time due to emerging symptoms suggesting an alternative disorder (such as "progressive supranuclear palsy").

Although **Parkinson disease affects more than mobility,** it is referred to as a **"movement disorder"** since the clinical diagnosis is based on the presence of specific abnormalities of movement and motor function:

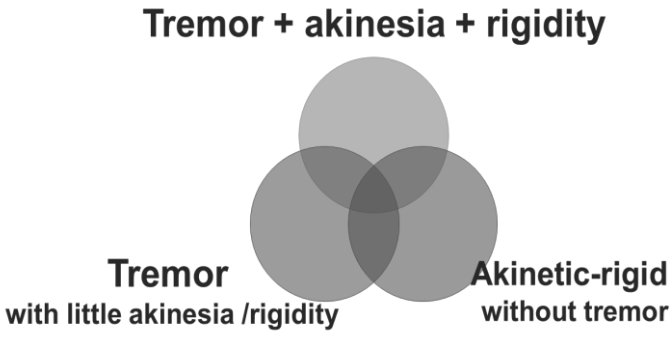
"Cardinal signs of PD":

- Slowness of movement (bradykinesia)
- Tremor at rest
- Rigidity – stiffness ("cogwheel rigidity")
- Abnormal gait and posture



Parkinson disease is a heterogeneous disorder! Clinical motor subtypes include:

- **"classic PD":** tremor + rigidity + bradykinesia
- **"tremor dominant PD":** prominent tremor with little rigidity or bradykinesia
- **"akinetic rigid PD":** rigidity and bradykinesia without tremor (often characterized by postural instability and gait disorder)



Early motor symptoms in “classic PD”

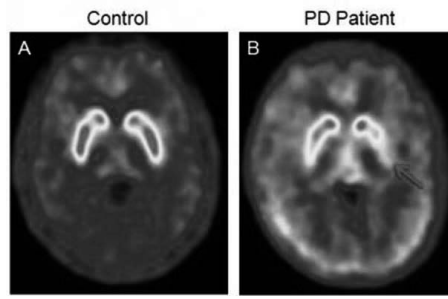
- The patient often reports that tremor was the initial symptom.

however

The physician is often struck by the immobile features (“**bradykinesia**”) of which the patient may be unaware:

- “masked” facial expression
- decreased blink frequency
- decreased arm swing when walking
- slowed gait with shortened stride
- sitting still without squirming
- fingers held in flexion - adduction

Asymmetry in Parkinson disease



- Motor signs and symptoms are almost always asymmetric in Parkinson disease
- The asymmetry is unrelated to the patient’s handedness
- Asymmetry persists throughout the course of the disease
- Dopamine imaging studies (such as dopamine transporter scans or PET scans) reveal greater loss of dopamine contralateral to the more affected side

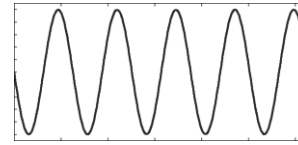
Tremor is often the symptom that brings the patient to seek medical attention

Although the general public associates Parkinson disease with tremor:

- Tremor is **not** always indicative of Parkinson disease
  (there are many other common causes of tremor, such as "**essential tremor**" and "**medication induced tremor**")
- Tremor is not a major symptom in every case of Parkinson disease
- Tremor is never the only sign in persons with Parkinson disease

Evaluating patients with tremor

Tremor is an **"involuntary, rhythmical, oscillation of a body part"** (and must be distinguished from other hyperkinetic movements such as myoclonus, dystonia, asterixis, or chorea)**.**



When examining patients with tremor it is useful to determine whether the tremor appears

- At "rest" or "repose":
  "rest tremor"
- When holding a posture (holding the hands outstretched):
  "postural tremor"
- Upon movement:
  "kinetic or action tremor"

Classification of tremor helps diagnosis

“rest tremor” is associated with parkinsonian disorders and refers to tremor in a limb or body part that is not being voluntarily activated:

Examples of “rest tremor”:

- Tremor in fingers or hand when seated with hands in lap
- Foot tremor while seated
- Hand tremor while walking with arms and hands at side

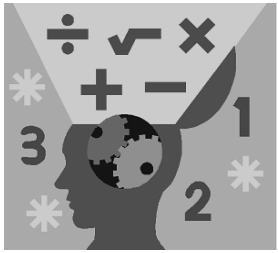
“postural” and “kinetic tremors” are most often associated with “essential tremor” and other non-parkinsonian disorders

“Rest tremor” is associated with **Parkinson disease** and other **parkinsonian disorders**

- The tremor may be **subtle** and **intermittent** in many cases and **prominent** in others
- Rest tremor can affect fingers, hand, foot, and occasionally jaw, lips, or tongue
- The rest tremor in PD is usually asymmetric or unilateral
- Rest tremor is usually suppressed when the affected limb is in motion

Techniques to elicit subtle "rest tremors" during the neurologic examination:

Observe the patient closely as subtle rest tremors often appear while:



- Performing mental tasks
  (for example, while doing "serial 7s")
- Discussing emotionally charged issues or under stress
- Moving the contra-lateral limb
  (for example, during "finger-nose-finger testing" a rest tremor might appear in the contralateral limb that is not being voluntarily moved)
- Walking
  (a unilateral hand tremor might appear, often accompanied by decreased arm swing of the affected limb)

The "re-emergent" tremor in PD

- PD patients with prominent rest tremor may also develop a postural tremor in the outstretched hand that emerges after a latency of a few seconds
  (referred to as **"re-emergent tremor"**)
- **This can potentially be confused with the postural tremor of "essential tremor"** (which typically occurs in the outstretched hands without latency)

The “re-emergent” postural tremor of PD

All tremors are potentially embarrassing to the patient, but unless quite severe, rest tremors generally do not impede most activities.

However:

The re-emergent postural tremor of PD can interfere with activities that are often impaired by essential tremor and not affected by the typical PD rest tremor :

- Spilling liquids from a full cup or soup spoon
- Tremor while holding a book or newspaper
- Tremulous handwriting

“shaky heads”

- **HEAD TREMOR**
  (“yes-yes”, “no-no”, or “complex”)

may occur in **essential tremor** and **cervical dystonia** but **rarely** occurs in Parkinson disease.

However:

- **JAW, LIP, MOUTH** or **TONGUE TREMOR**

may occur in **Parkinson disease** and other **parkinsonian disorders**, but are **seldom** encountered in patients with essential tremor.

The severity of tremor commonly waxes and wanes:

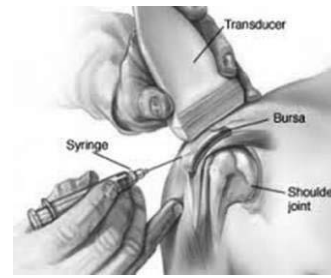
Patients with tremor will find that their involuntary movements are exacerbated by

- Stress
- Anxiety
- Excitement
- Anger
- Fatigue
- Mental activity
- Self consciousness
- Fever / systemic illness

Discussing this with patients helps them better understand and cope with their tremor.

"akinetic-rigid Parkinson disease": some PD patients have little or no tremor

- The diagnosis is usually unsuspected or delayed in the subset of PD patients who do not have tremor
- PD patients without tremor often are misdiagnosed !



Pain can be a symptom of PD:

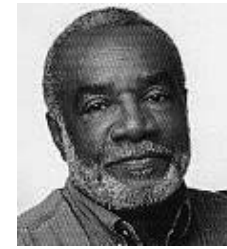
(for example, a painful rigid bradykinetic upper or lower extremity is easily mistaken for a "frozen shoulder", "capsulitis", "sciatica" and other orthopedic or musculoskeletal problems leading to inappropriate treatments)

- How do PD patients without tremor present to the physician?

The diagnosis is often missed or delayed in PD patients who do not have tremor:

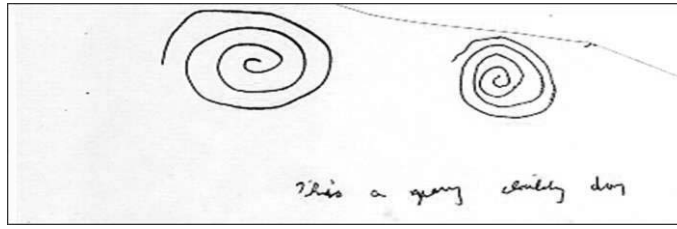
What symptoms do these patients experience?

- "I've slowed down tremendously"
- Trouble arising from a deep chair or sofa
- Slowed or shuffling gait / unsteadiness
- Decreased arm swing (usually unilateral)
- Discomfort, pain, or stiffness in a limb (often mistaken for an orthopedic problem)
- "my handwriting has gotten smaller" (micrographia)
- Change in facial *expression* ("masked face")
- Speech softer or slower
- REM sleep behavioral disorder
- Loss of olfaction



Handwriting in Parkinson disease

changes in writing are often an early feature of the disease



- Some patients have generally small handwriting.
- Some patients have "fatigable micrographia". (writing becomes progressively smaller as the sentence goes on)
- Some have writing that is still relatively "normal", but is "smaller than it used to be".
- Some note no change in handwriting.
- Patients with "emergent tremor" might have tremulous writing, but this is not the case in most PD patients.

“cogwheel rigidity” in Parkinson disease

“rigidity”: a stiffness and increased resistance to passive movement of a limb segment

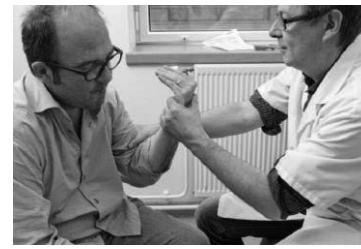
Ratchet-like **“cogwheel rigidity”** is typical of PD and parkinsonian disorders

but must be distinguished from

spasticity: “clasp knife” rigidity with hyper-reflexia

gegenhalten: rigidity is increased in opposition as force is increased

dystonia: stiffness with abnormal posture of limb, sometime waxing and waning, causing involuntary movements resembling tremor



A key symptom in diagnosing PD is bradykinesia (“slowed movement”)

To more confidently diagnose Parkinson disease the patient should have:

- Bradykinesia

Plus presence of at least 2 of the following features:

- Rest tremor
- Cogwheel rigidity
- Gait / balance problems
- Asymmetry of findings

Bradykinesia

Bradykinesia is a complex phenomenon that includes:

- **"bradykinesia":** slowness
- **"hypokinesia":** small amplitude of movements
- **"akinesia":** absence of movement (including slowed reaction time, because movement does not occur when expected)
- **dysrhythmic movement**

Bradykinesia (not rest tremor) **is viewed as the "sine qua non" of Parkinson disease**

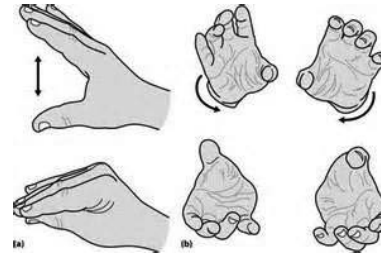
Bradykinesia is characterized by

- "slowness in the initiation and execution of voluntary movement"
- movements are also under-scaled for the required task
- A progressive reduction in speed and amplitude of repetitive motions
  (for example, while tapping fingers or tapping toes, the movements become slower and smaller)

Bradykinesia is more likely to cause disability in persons with PD than tremor.

Testing for bradykinesia in the office

- Repetitive finger tapping
- Repetitive hand opening
- Repetitive toe or foot tapping



Bradykinesia causes progressive decrease in speed and amplitude of movement during these tasks.

- Micrographia
- Reduced spontaneous movements, including facial muscles (“hypomimia”)
- Reduced gesticulation
- Stiff movements (“en bloc”)
- Reduced spontaneous movements “body bradykinesia”

“hypomimia” - “masked facial expression”

Bradykinesia of the facial muscles can lead to an *expressionless facial appearance* and a *blank stare.*

“Masked facial expression” is common in Parkinson disease and other parkinsonian disorders.

Unfortunately, this appearance can mistakenly lead others to assume that the patient is

unhappy, depressed, bored, unfriendly, disinterested, or lacking in empathy.

Changes in speech in Parkinson disease

Common features of speech in patients with early PD include:

- **Reduced vocal loudness** (hypophonia often accompanied by mild dysarthria)
- **Mono-loudness** (monotone)
- **Mono-pitch / dysrhythmic speech**

Speech problems are mild in the first several years of Parkinson disease, becoming more notable as the disease progresses (at which time dysphagia is often also a potential problem).

Eye findings associated with PD

- Infrequent blinking of the eyelids (“stare”)
- Widening of the palpebral aperture
- “blepharoclonus” (fluttering of eyelids when eyes are gently closed)
- Eye movements are normal except for reduced convergence in some cases
- Saccades are normal (slowed saccades suggest the likelihood of an alternative diagnosis, such as progressive supranuclear palsy)
- Parkinson disease is not associated with nystagmus (nystagmus suggests a vestibular or cerebellar disorder)

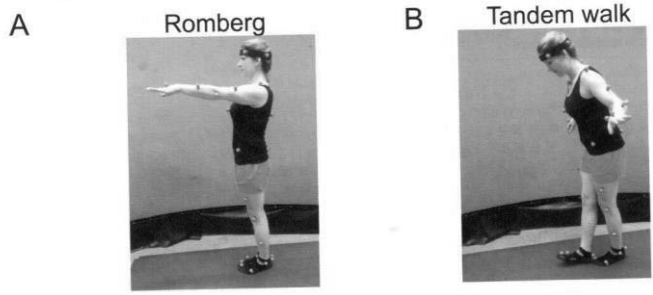
Gait in Parkinson disease

- Difficulty arising from chair
- Slowed with short steps but narrow base
- Decreased arm swing
  (unilateral: on the more affected side)
- “en bloc” and multi-step turning
- Stooped posture
- Propulsion (speeding up involuntarily)

Later in the disease course:

- Postural instability with retropulsion: falling backward with inability to catch oneself
- Delayed gait initiation
- “freezing of gait” and motor blocks

Gait in Parkinson disease



Retropulsion and bradykinesia cause many PD patients experience difficulty arising from a deep chair or sofa. Several attempts to arise might be necessary, or some might need to push on the arms of the chair with their hands in order to stand up (which can be misinterpreted as reflecting proximal muscle weakness).

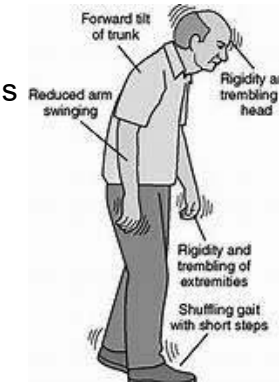
The Romberg test and tandem gait should be “normal for age” in uncomplicated PD.

Gait in Parkinson disease

- "tandem gait" is performed appropriately well for age, even in rather advanced PD
- Romberg test is steady

"Broad-based gait" suggests other conditions such as concomitant
cerebellar dysfunction,
vestibular disorders, or
"sensory ataxia" (as seen in severe peripheral neuropathy or cervical myelopathy)

- Unilateral decreased arm swing is very typical in PD, but can be misinterpreted as a sign of "stroke"
- A subtle hand tremor on the affected side is often noted while walking



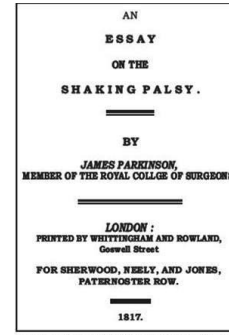
"propulsion" in Parkinson disease

James Parkinson (1817) commented on:

"a propensity to bend the trunk forward and to pass from a walking to a running pace"

Patients report that they might begin moving forward too quickly and have difficulty catching themselves (particularly when they are walking downhill).

If the patient is not cautious, propulsion or retropulsion can lead to falls.


AN
ESSAY
ON THE
SHAKING PALSY.
BY
JAMES PARKINSON,
MEMBER OF THE ROYAL COLLGE OF SURGEONS.
LONDON:
PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street
FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.
1817.

An Essay on the shaking Palsy is a short pamphlet written in 1817 by the London physician, James Parkinson. In this monograph, that quickly become hard to find, he described a series of six patients, several whom he never examined, but only saw on the London streets. The hallmarks of the condition that would later bear his name were tremor, slowness, and gait difficulty. He guessed that the location of the lesion was the cervical cord or the medulla oblongata, but did not perform autopsies.

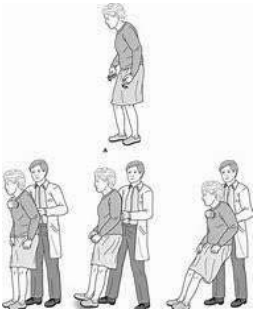
“festinating gait” and “freezing of gait”

Festination refers to:
“a tendency to walk with high-cadence short steps, and a center of gravity well in front of the feet”

“freezing of gait” refers to:
feet being “stuck” and unable to move when trying to initiate or sustain gait.

These are risk factors for falls, but fortunately do not affect every patient, and are not prominent features early in the course of PD.

Retropulsion and the “pull test”



- Propulsion (walking too fast and falling forward) and retropulsion (falling backward) occur in Parkinson disease and other parkinsonian disorders
- These symptoms increase the risk of falling
- Retropulsion can be evaluated by performing the “pull test”
- Pull backward with good force, but be prepared to catch the patient if necessary when performing the “pull test”

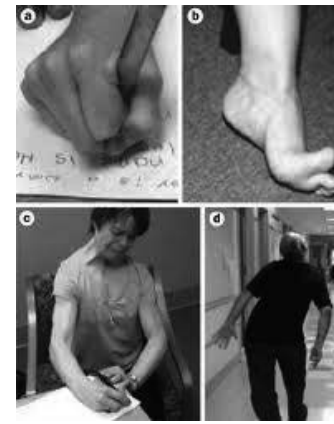
Dystonia in Parkinson disease

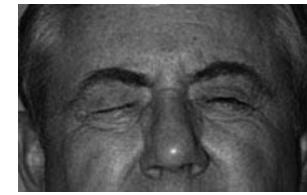
Common dystonic symptoms include:

- Toes: curling or extending
- Feet: inversion or plantar flexion
- Hand: fingers and thumb extended with partial flexion at MCP joints
- Cervical dystonia
- Eyes: blepharospasm

Dystonia is common in younger onset untreated PD patients.

Dystonia also occurs in patients of any age with more advanced PD, often related to “wearing off” of medication effects between doses.





“kinesia paradoxica”

“Improvement in motor activity in response to excitement or an emergency”

For example:

- In the physician’s office, the spouse will often comment:

“he is not shuffling now -
he never walks or moves this well at home!”

To obtain a more reliable assessment of how people are functioning on a daily basis, try to assess gait and other movements when the patient does not know that they are being observed.

Diurnal variations in Parkinson disease

For some patients

- Symptoms are much better in the morning **("sleep benefit"):**

Upon awakening in the morning some patients report that they feel as if they do not have Parkinson disease.

- Symptoms gradually return as the day progresses (which patients may erroneously attribute to an adverse effect of their PD medication)

Sleeping well at night can be beneficial for improving motor symptoms, particularly in patients with early PD.

"United Kingdom brain bank clinical diagnostic criteria for diagnosing Parkinson disease" has very high accuracy in predicting pathologic changes of PD at autopsy

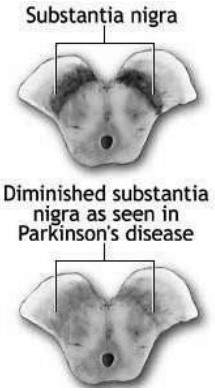
Step 1: diagnosing a Parkinsonian syndrome

- **Bradykinesia**
- At least one of the following:

  Muscular rigidity

  4-6 Hz rest tremor

  postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)

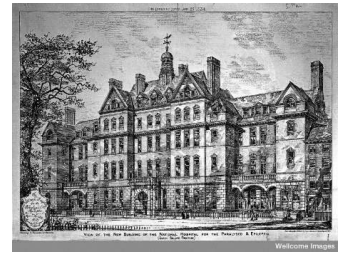


(note that bradykinesia and not rest tremor is the mandatory clinical sign for diagnosing PD in the UK brain bank criteria)

"United Kingdom brain bank clinical diagnostic criteria for diagnosing Parkinson disease"

Step 2: Exclusion criteria for Parkinson's disease

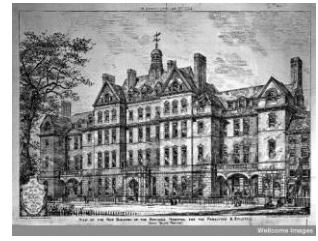
- Repeated strokes with stepwise progression of parkinsonian symptoms
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- Sustained remission
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia
- Babinski signs
- Tumor or hydrocephalus on brain imaging study
- Negative response to adequate doses of levodopa



"United Kingdom brain bank clinical diagnostic criteria for diagnosing Parkinson disease"

Step 3: supportive prospective positive criteria for Parkinson disease (3 or more required in combination with features in step 1)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most prominently
- Excellent response to levodopa therapy
- Development of levodopa-induced dyskinesia
- Favorable response to levodopa for over five years
- Clinical course of 10 years or more



PD is more than just a "*movement disorder*"

abnormal movement is often just "the tip of the iceberg"

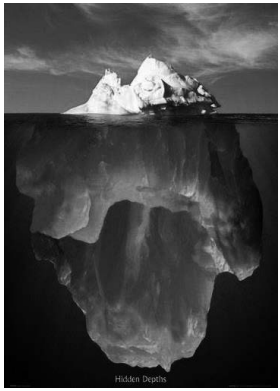
Autonomic function

- Orthostatic hypotension
- Bowel, bladder, sexual function

Neuropsychiatric problems

- Depression / Anxiety
- Apathy and behavioral changes
- Cognitive impairment

Sleep disorders



(subsequent sections in this primer review the important "non-motor" aspects of Parkinson disease)

Divulging the diagnosis of Parkinson's disease:

Newly diagnosed patients often debate whether **"to tell" or "not to tell"** family, employers, friends

<u>Do not tell</u>:

- "It is no-one's business"
- "I do not want people to feel sorry for me or patronize me"
- "I do not want people to scrutinize me"
- "It may affect my job or clients"
- "I don't want people to think I am infirm or old"

<u>Tell</u>:

- "There is nothing to be ashamed of"
- "There will be less stress, as I will not have to try to hide my symptoms"
- "People will better understand my situation"
- "People won't gossip about what is wrong with me"
- People might be angry with me for not being forthright

PROGNOSIS
in Parkinson Disease

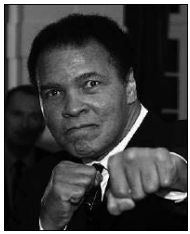
Information that is true at the population level is difficult to translate to the individual patient. Each case is different, so that prognostication is subject to error. The only doctors that can render perfect prognostication are the doctors on television soap operas (and that's because they have a script). Parkinson disease is a neurodegenerative disorder that slowly worsens over time, but there is no definite script for each patient. "No cure" does not mean "no hope".

We have all heard the old saying
"if you've seen one, you've seen them all".
However, if you've seen **<u>one</u>**
Parkinson disease patient …

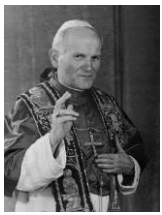
you've seen **<u>one</u>** Parkinson disease patient!

PD symptoms and problems vary widely.

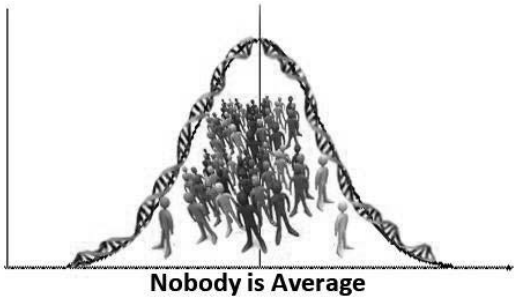
(Each patient confronts a unique set of challenges. The topics discussed in this primer will affect some but not every patient.)







Prognosis in Parkinson disease



Patients want to know:

- **How long?**
- **How well?**

Parkinson disease is a neurodegenerative disorder that slowly worsens over time. The symptoms and rate of progression are highly variable from patient to patient.

It is possible to keep most PD patients in the mainstream of life for many years after diagnosis.

Two types of patient:

When asking patients about whether they are experiencing a specific symptom, you expect them to answer:

"yes" or "no"

(or perhaps "maybe")

However, some patients reply:

"not yet !"

Reassure your patients that despite what they may have inferred from reading blogs or websites, everyone with PD does not experience the same symptoms or the same clinical course.

Good mental health is the key to coping with a chronic condition.

Discourage patients from becoming "not yetters".

What should physicians tell their patients?

Every person is unique!

Information that is true at the population level is difficult to translate to the individual patient, nevertheless

- PD is a slowly progressive disorder that will alter their lives

however

- Many effective treatment options are available

Remind patients:

"Pessimists and optimists develop the same illnesses but lead very different lives!"

Factors affecting long-term prognosis in PD

some general guidelines

"<u>negative indicators</u>":

- Postural instability and bradykinesia without tremor
- Falling
- Apathy
- Cognitive decline / dementia
- Depression / anxiety
- Dysphagia
- Orthostatic hypotension

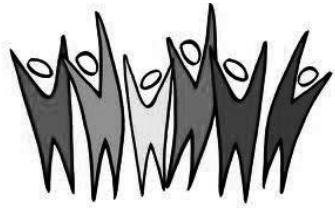
"<u>positive indicators</u>":

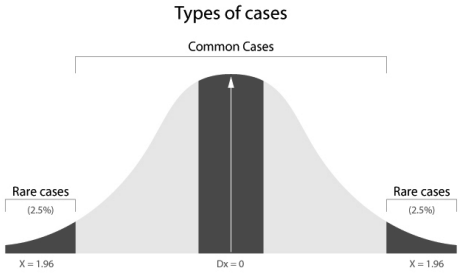
- Prominent tremor without gait disorder or bradykinesia
- Normal cognition
- Positive attitude
- Participation in exercise programs

"Early onset Parkinson disease" (20s-40s) is associated with slower progression, and fewer cognitive symptoms. However, these patients have an increased susceptibility to depression, anxiety, dyskinesias, "impulse control disorders", and dopamine dysregulation syndrome.

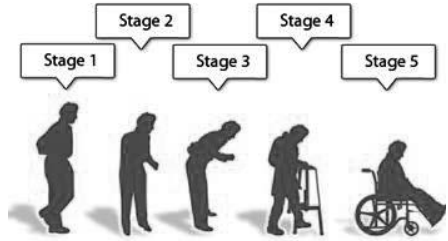
What we call "Parkinson disease" is actually a syndrome, not one disease

- Many varieties of symptoms
  motor and **non-motor** symptoms
- Multiple factors affect the occurrence and clinical expression of symptoms
  aging, genetics, epigenetics, environmental factors, toxins
- Variable prognosis
  the variety of symptoms and the rate of decline varies





Why does Parkinson disease ***worsen*** over time ?



1. Progressive degeneration of the nigro-striatal dopaminergic system and other brain pathways
2. Emergence of non-dopaminergic motor problems
3. Emergence of significant non-motor problems
4. Side effects of treatment
5. Concomitant medical and age related problems have a major impact on clinical outcomes and prognosis.

The rate and extent of decline is variable from patient to patient. Every patient does not end life at “stage 5” in a wheelchair or nursing home.

Life expectancy in Parkinson disease

Patients often ask

“is Parkinson disease a fatal condition?”

- The life expectancy of patients with PD who receive appropriate treatment and who do not develop significant cognitive decline is similar to survival rates in the general population.
- PD dementia and psychosis are associated with a significantly shortened life expectancy.

“quality of life” in Parkinson disease

- Parkinson disease is a “*life sentence*” not a “*death sentence*”.

The importance of good mental health cannot be overlooked:

- The “quality of life” in PD often depends as much or more on the management of the potential psychiatric and behavioral aspects of the disease than the severity of motor symptoms.

Conditions that mimic or can be mistaken for Parkinson disease

The differential diagnosis for “parkinsonism” is extensive, and diagnostic errors are common. Even after many years of follow-up, some patients with seemingly typical Parkinson disease develop symptoms suggesting an alternative diagnosis (such as “progressive supranuclear palsy”).

Does everyone who is “parkinsonian” have Parkinson disease ?

NO !

There are many other conditions that present with signs and symptoms that might mimic Parkinson disease.

Diagnostic certainty is not possible during life. 10- 20% of patients initially diagnosed with Parkinson disease by experienced clinicians will eventually be found to have another related neurologic disorder when followed clinically over time (or at autopsy) !

Why is it important to identify conditions that can mimic Parkinson disease ?

- Misdiagnosis is common, even among “experts”.
- Atypical clinical features may appear months to years after initial presentation: the diagnosis of Parkinson disease should be reconsidered at each visit.
- The prognosis and response to treatment of the disorders that mimic PD is different than in true Parkinson disease.
- Clinical trials for “neuroprotection” or new PD treatments are often confounded by the inclusion of patients who actually have other disorders.

10 common pitfalls in diagnosing Parkinson disease

1. Confusion with essential tremor
2. “drug-induced parkinsonism” is often misdiagnosed as Parkinson disease
3. Delayed diagnosis or misdiagnosis of PD patients without tremor
4. Other neurodegenerative disorders mimicking Parkinson disease
   (e.g. progressive supranuclear palsy, multiple system atrophy, cortico-basal degeneration)
5. “lower half parkinsonism” (parkinsonian gait disorder without other parkinsonian symptoms) due to cerebrovascular disease (often referred to as “vascular parkinsonism”)..

10 common pitfalls in diagnosing Parkinson disease

6. Parkinsonism presenting with dementia (“dementia with Lewy bodies”)
7. Gait disorders, hypomimia, and apathy due to “normal pressure hydrocephalus” (“symptomatic adult hydrocephalus”)”
8. Mild “parkinsonian signs”, atypical tremors, and gait disorders seen in elderly patients without true Parkinson disease
9. Young onset PD patients presenting with prominent dystonia
10. Sensory, painful, or unilateral lower extremity presentations of PD

“All that glitters is not gold”
“All that shakes is not Parkinson disease” !

Many persons who develop tremor erroneously assume that they have Parkinson disease.

“Essential Tremor”
(a very common condition affecting approximately 2-3% of people by age 70) is often misdiagnosed as Parkinson disease.

The prognosis and treatment of essential tremor and Parkinson disease are quite different. It is important to make an accurate diagnosis and carefully explain to the patient the differences in symptoms and prognosis between essential tremor and PD.

Many people ***SHAKE***
but most do **not** have Parkinson disease

Essential tremor is characterized by

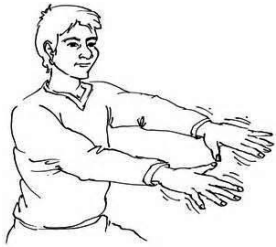
- **Postural** and **kinetic tremor** of hands (occasionally head or voice tremor) without bradykinesia or gait disorder.

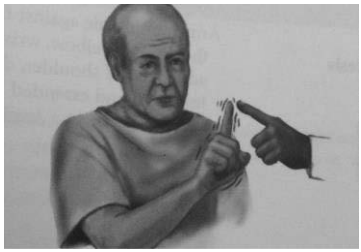
Essential tremor needs to be accurately differentiated from

Parkinson disease which causes

- Asymmetric **rest tremor** of fingers, hand, or foot (plus other motor symptoms: bradykinesia, gait disorder, cogwheel rigidity, and non-motor symptoms)

Tremors associated with **"essential tremor"** rather than Parkinson disease





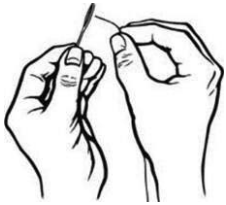
"<u>Action tremors</u>":

- **Postural tremor:** tremor seen in the outstretched hands (vertical tremor not pronation – supination)
- **Kinetic tremor:** tremor with voluntary movement

  (for example, tremor when writing, pouring water from cup to cup, or on "finger-nose-finger testing")

Some patients with very longstanding ET might also develop a mild rest tremor without other signs of Parkinson disease.

When is "essential tremor" most annoying?



- Difficulty drinking water from a full glass
- Difficulty drinking soup with a spoon
- Tremulous illegible handwriting
- Trouble using a computer "mouse"
- Shaking when applying makeup
- Impaired fine motor activities (e.g. threading a needle)

Parkinson disease does not affect these activities in the same way, except in the small sub-group of PD patients with severe "emergent tremor".

“indeterminate tremor”

There is a group of patients with

- Unilateral or very asymmetric tremor
- Position or task-specific tremor (and therefore more likely to be disabling)
- Pronation-supination rather than vertical tremor

But

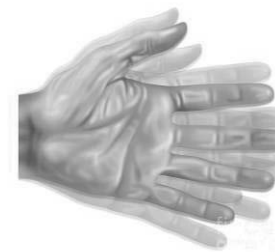
- Without (at least yet) frank dystonia
- Without (at least yet) bradykinesia or gait disorders

These patients should be labelled as having “indeterminate tremor”, thereby avoiding misclassification as essential tremor or premature diagnosis of “dystonic tremor” or Parkinson disease.

Clinical follow-up is appropriate for these patients. This is a situation where a dopamine transporter scan (DaT scan) could help clarify the differential diagnosis.

“rest tremor” in essential tremor

- In some long-standing cases of essential tremor the hand tremor may spill over into the resting state and mild cogwheel rigidity might also be noted.



However:

- In ET the “action tremors” remains more prominent than the rest tremor.
- While walking:
  - In ET: arm swing is normal and any rest tremor is not apparent. There is no shuffling or unsteadiness.
  - In PD: arm swing is diminished and rest tremor is often enhanced while walking.

“Postural tremors” resembling “essential tremor” can be caused or aggravated by :

- *Medications*:
  - lithium
  - valproic acid
  - amiodarone, mexiletine, tocainide
  - bronchodilators, theophylline, terbutaline
  - cyclosporine, tacrolimus
  - stimulants (caffeine, amphetamine, steroids)
  - “serotonin syndrome”
- *Metabolic disorders*
  - thyrotoxicosis
  - hypoglycemia
  - renal, hepatic, or endocrine disorders
- *Alcohol or drug withdrawal syndromes*
- *Anxiety – “enhanced physiologic tremor”*

Differential diagnosis of “action tremor”

- Essential tremor
- Enhanced physiologic tremor
- Thyrotoxicosis
- Medication induced tremor
- Re-emergent postural tremor of PD
- Serotonin syndrome
- Withdrawal syndromes
- Metabolic tremor
- Cerebellar tremor
- Fragile X tremor ataxia syndrome
- Dystonia with tremor (dystonic tremor)
- Wilson’s disease
- Orthostatic or task specific tremor
- Indeterminate tremor
- Psychogenic tremor

Differential diagnosis of "parkinsonism":

Parkinson disease:

"classic": tremor + bradykinesia + rigidity
tremulous variant
akinetic – rigid variant

Secondary parkinsonism:

medication induced parkinsonism
toxin induced parkinsonism
vascular parkinsonism

These disorders are not rare "zebras"

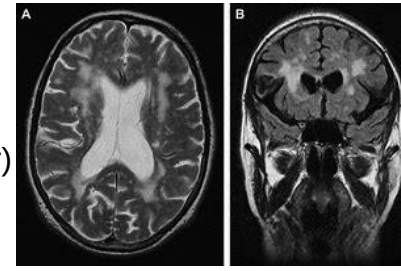
"Parkinson-plus" degenerative disorders
("parkinsonian" symptoms **plus** additional atypical features)**:**

progressive supranuclear palsy
multiple system atrophy
cortico-basal degeneration , et. al.

Mild "parkinsonism" in older adults

Mild parkinsonian signs are present in nearly 50% of community dwelling people by age 85, characterized by:

- "stooped posture" and/or
- shuffling gait and/or
- "slowness" and/or
- tremor (usually postural tremor and not parkinsonian rest tremor)



The mild parkinsonism in elderly persons without true Parkinson disease is often caused by other neuronal degenerative processes or extensive microvascular disease.

“red flags” suggesting a “parkinson - plus” disorder rather than true Parkinson disease

Early onset of:

- Postural instability and falls
- Shuffling-freezing gait without other motor symptoms
- Significant speech problems
- Cognitive decline or hallucinations
- Prominent autonomic problems (e.g. severe orthostatic BP, incontinence)

and / or :

- Symmetrical findings
- Axial > appendicular rigidity
- Absence of “rest tremor”
- Slowing of saccadic eye movements
- Apraxia
- Cerebellar ataxia

Movement Disorder Society **exclusion criteria** for the diagnosis of Parkinson disease

- Unequivocal cerebellar abnormalities (e.g. appendicular or gait ataxia, cerebellar oculomotor abnormalities)
- Downward supranuclear gaze palsy or selective slowing of downward saccades
- Parkinsonian features restricted to the lower extremities for more than 3 years
- Treatment with a dopamine receptor blocker or dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism

Movement Dis 2015; 30: 1591-601

Movement Disorder Society **exclusion criteria** for the diagnosis of Parkinson disease

- Absence of observable beneficial response to high dose levodopa despite at least moderate severity of motor symptoms
- Normal functional neuro-imaging (PET scan or DaT scan) of the pre-synaptic dopamine system
- Unequivocal cortical sensory loss, limb apraxia, or progressive aphasia
- Documentation of an alternative condition known to produce parkinsonism plausibly connected to the patient's symptoms or suspected to be more likely than PD

Movement Dis 2015; 30: 1591-601

"progressive supranuclear palsy" (PSP) is the most common "parkinson - plus" disorder

Clinical features suggesting PSP:

Basal ganglia:

- Loss of balance / retropulsion / falls
- Bradykinesia
- Prominent axial rigidity (neck rigidity) (unlike PD where limb rigidity is more notable)

Figure 1: Patient showing loss of vertical gaze pretreatment with increased neck extension

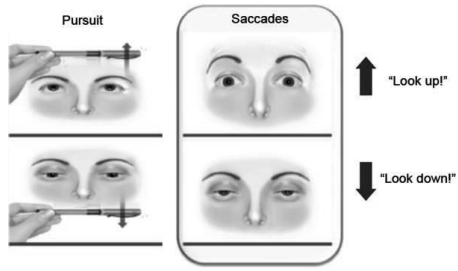
Brainstem:

- Supranuclear gaze problems: slowed vertical saccades and eventual loss of voluntary vertical eye movements
- Dysarthria / dysphagia

Cognitive / behavioral:

- Bradyphrenia
- Frontal behavioral changes

Oculomotor abnormalities in PSP



- Slowing of downward saccades is the initial oculomotor sign (but is not a finding noted early in the disease in many cases)
- Eventually voluntary vertical eye movements are very impaired with preserved vestibulo-ocular reflex (the "doll's eyes maneuver")
- Horizontal saccades become slow and hypometric
- Be sure to test "**saccades**" not just "pursuits" ("pursuit" eye movements can be relatively spared until later in the disease)
- "square wave jerks" are often present, but are a "non-specific" finding that can also be seen in PD and other conditions

Autopsy studies have shown that

"progressive supranuclear palsy" is a disorder with many different clinical presentations:

Phenotype:	**Designation**:
• Classic phenotype (with prominent early oculomotor abnormalities)	• PSP- Richardson syndrome
• Parkinson disease-like (without early oculomotor signs)	• PSP-parkinsonism
• Pure akinesia	• PSP-akinesia with gait freezing
• Asymmetric parkinsonism with apraxia	• PSP-corticobasal syndrome
• Frontal predominant dementia	• PSP-frontotemporal dementia

Retropulsion: the “I - bar sign” in PSP

Persons with PSP might promptly fall backward on the “pull test” (unlike early or moderate stage PD patients who will make a corrective step when pulled backward).

Be prepared to catch patients when performing the “pull test”!

PSP is the most common degenerative disease that potentially mimics PD.

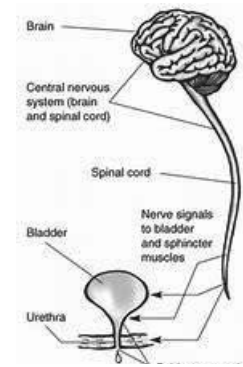
The typical eye movement signs of PSP may not appear until many years after other symptoms, eventually leading the physician to revise the diagnosis from PD to PSP in perhaps 5% of cases!

“multiple system atrophy” (MSA) can mimic Parkinson disease

- In patients with MSA, parkinsonian motor signs are accompanied by **prominent autonomic symptoms** early in the course:
  - orthostatic hypotension / syncope
  - constipation
  - incontinence of urine / erectile dysfunction

Caveat: mild dysautonomia is common in PD, and most parkinsonian patients with orthostatic hypotension do **not** have MSA.

- REM sleep behavioral disorder is common in both MSA and PD
- **Cerebellar** and **pyramidal signs** are often noted in MSA (but not in PD)
- “dropped head” and camptocormia are more common in patients with MSA than PD



Clues to diagnosis of MSA

- Oro-facial dystonia beginning shortly after starting levodopa should raise the suspicion of MSA rather than PD
- Unlike PD, olfaction is usually preserved in MSA
- Atonic bladder is common in MSA not PD
- Pseudobulbar emotional incontinence, camptocormia, and antecollis are all more common in MSA than PD
- Brainstem respiratory centers can be affected in MSA, causing **nocturnal stridor** (screeching inspiratory sounds): if suspected, a "sleep study" should be performed as there is potential risk of death due to central respiratory failure!

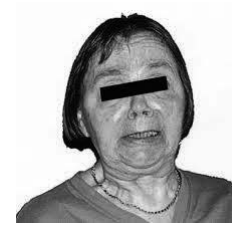
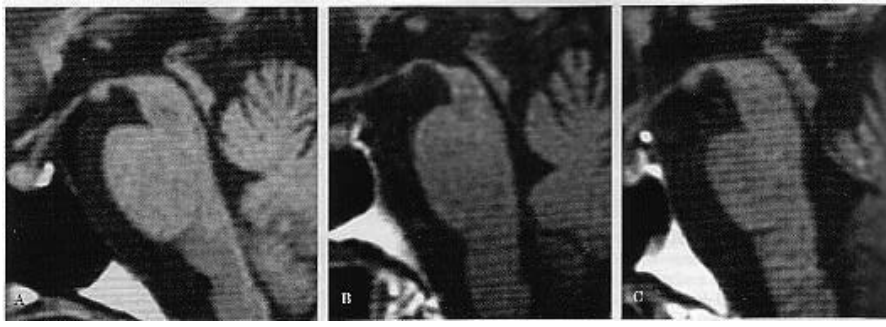


Fig. 1. Disproportionate antecollis of a patient with MSA-P.

MRI brain imaging can sometimes be informative in atypical parkinsonian conditions



Mid-sagittal MR images of brainstem:

a. Parkinson's disease: "normal" pons, midbrain
b. PSP: midbrain atrophy ("hummingbird sign")
c. MSA with parkinsonism: marked atrophy of pons

“corticobasal syndrome” can mimic PD

Begins in 50s or 60s with variable combination of progressive signs:

- Asymmetric movement disorder:

unilateral parkinsonism, unilateral dystonia, unilateral rigidity, or focal myoclonus -

Relatively little improvement with L-DOPA

Additional features:

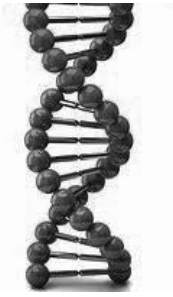
- “alien limb” phenomenon
- Cortical sensory loss
- Ideomotor apraxia
- Gradual cognitive impairment

This clinical syndrome is associated with “cortico-basal degeneration” and other brain pathologies including PSP !

Evaluating “atypical presentations of atypical parkinsonism”

- Mean ages of onset of the most common conditions:
  - Progressive supranuclear palsy 63
  - Multiple system atrophy 60
  - Cortico-basal degeneration 50

A positive family history of atypical parkinsonism, or an unusually early age of onset raises the possibility of a genetic or metabolic disorder:



- fragile X tremor ataxia syndrome
- progranulin (PGRN) mutations
- microtubule associated tau (MAPT) mutations
- Niemann- Pick type C disease
- Gaucher’s disease type 1
- mitochondrial disorders
- spino-cerebellar ataxia types 2, 3, 12, 17, or 21

are some of the genetic disorders that can occasionally manifest symptoms mimicking parkinsonian disorders.

Do not overlook “drug induced parkinsonism” !

caused by medications that block or deplete dopamine

Common culprits include:

Gastrointestinal / nausea medications:

- Metoclopramide
- Prochlorperazine

Antipsychotic medications:

“Traditional” neuroleptics

- haloperidol, perphenazine, et. al.

“Atypical” (2nd generation) neuroleptics:

- risperidone, olanzapine, ziprasidone, aripipazole, et. al.

Other medications:

- tetrabenazine, reserpine

“Drug induced parkinsonism” (DIP)

May be indistinguishable from Parkinson disease, including akinetic rigidity without tremor, but there may be some atypical clinical features -

Clues to diagnosis of DIP include:

- Exposure to a dopamine blocker !
- Presence of another movement disorder, such as **akathisia** or **tardive dyskinesia**
- Symmetrical signs (unlike PD which is usually asymmetric)
- “action tremor” may be more prominent than “rest tremor”
- “rabbit syndrome”: a low frequency high amplitude jaw tremor
- A dopamine transporter scan (DaT scan) is usually not needed, but would be normal in DIP

Managing drug induced parkinsonism (DIP)

- Eliminate the offending drug!

  however

be aware that DIP can persist
for many months after drug withdrawal

- If the patient's condition requires neuroleptic therapy, consider clozapine or quetiapine (which, unlike the other 2nd generation neuroleptics, do not cause or exacerbate parkinsonism).
- Anticholinergics may help reduce rest tremor, but can exacerbate psychiatric symptoms and should be avoided.
- Carbidopa/levodopa is not helpful in treating the motor symptoms of DIP unless the patient also has PD.

Prognosis of "drug induced parkinsonism":

"Gradual resolution of parkinsonian signs after the dopamine blocking drug is completely withdrawn."

However:

Although the **"half-life"** of the drug may just be hours or days, the **"biologic effect"** of dopamine blocking drugs can last for **weeks** to **months**:

Drug induced parkinsonism can persist for six months or longer after drug withdrawal!

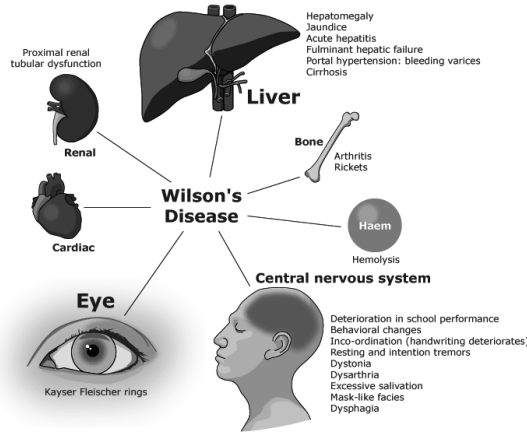
Therefore, when taking a drug history, be sure to ask about all medications taken over the preceding 6 months or more.

If parkinsonian symptoms persist for over a year after medication withdrawal, it is likely that the patient had underlying Parkinson disease (perhaps exacerbated by dopamine blocking medications).

Consider Wilson's disease, a very serious but potentially reversible autosomal recessive disorder of copper metabolism **in younger patients with movement disorders**

Neurological features of Wilson's disease:

- Parkinsonism 62%
- Dystonia 35%
- Dysarthria
- Cerebellar 28%
- Pyramidal signs 16%
- Chorea 16%
- Athetosis 2%
- Myoclonus 2%
- Behavioral abnormalities 16%



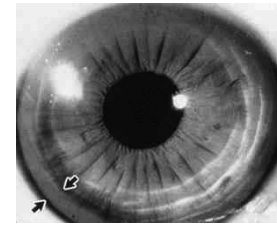
Medicine 2007; 86: 112-121

Diagnosing Wilson's disease

Kayser-Fleischer rings (brownish discoloration at the corneo-scleral junction) are present in:

- Neurological patients 100%
- Hepatic patients 86%
- "pre-symptomatic" cases 59%

A slit-lamp examination by an experienced ophthalmologist is necessary to exclude the presence of a Kayser-Fleischer ring



Serum ceruloplasmin:

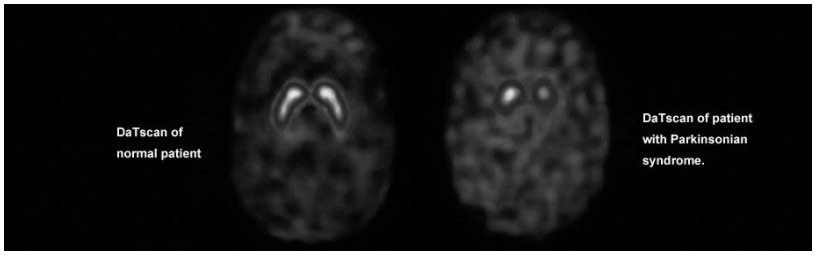
- Decreased in 93%

24-hour urinary copper

- Increased in 70%

What about the Dopamine transporter (DaT) scan ?

(ioflupane I_{123} images the presynaptic dopamine transporter in the striatum)



- Abnormal in Parkinson disease, but also abnormal in other degenerative parkinsonian syndromes: PSP, MSA, and CBD
- Normal in essential tremor, “drug-induced parkinsonism”, and psychogenic parkinsonism
- May be normal or abnormal in “vascular parkinsonism”

Careful clinical assessment makes the DaT scan unnecessary in the vast majority of cases!

TREATING the MOTOR SYMPTOMS of PARKINSON DISEASE

There are effective options to treat the motor symptoms of Parkinson disease. Optimal use of current medical and surgical treatments assures the best outcomes for our patients.

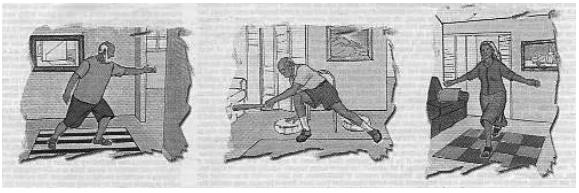
Treating Parkinson disease:

What treatment should you recommend for every Parkinson disease patient?

Exercise !

Long term outcomes are better in PD patients who participate in exercise programs on a regular basis. Exercise helps patients maintain mobility, dexterity, and balance, and also has potential benefits on mental health.

Exercise is an important part of the treatment regimen for everyone with Parkinson disease



Exercise improves long term outcomes, but programs must be tailored to the patient's abilities and needs.

Aerobic (vigorous) exercise:

- Brisk walking
- Swimming
- Treadmill / bicycle
- Dance
- Boxing

Sedentary exercise:

- Postural exercises
- Balance training
- Flexibility exercises
- Recumbent exercises
- Strengthening exercises

Exercise classes for Parkinson disease

- People who are not accustomed to exercising will often procrastinate or make excuses, and are less likely to begin a regular or appropriate PD exercise program at home.
- There is a natural tendency for people to over-estimate the amount of exercise they do at home.
- Participation in an appropriate supervised class for persons with PD improves compliance with an exercise regimen, and has both physical and social benefits.

"Symptomatic treatment": When should medication for treating the motor symptoms of Parkinson disease be initiated?

- People with very mild symptoms do not necessarily have to be started on medication for Parkinson disease.

(but might consider participating in a clinical trial of an experimental "neuroprotective" agent)

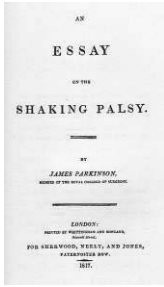
However, if symptoms
- interfere with employment, or
- interfere with daily activity, or
- impair balance, or
- cause embarrassment

starting medication to reduce the motor symptoms of PD should be recommended.

How were medications to reduce the motor symptoms of PD discovered, and how do they work?

Spend time to educate your patients about the medications used to treat the motor symptoms of Parkinson disease. Knowledgeable patients are more likely to use their medications appropriately, thereby improving compliance and clinical outcomes.

Brief review of the history of Parkinson disease



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

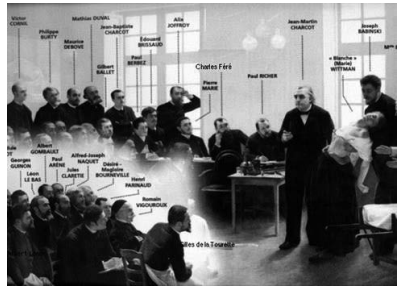
PRINTED BY WHITTINGHAM AND ROWLAND,

Dean-street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

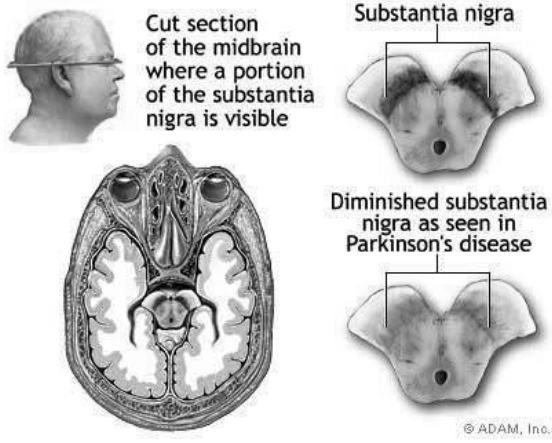
1817.

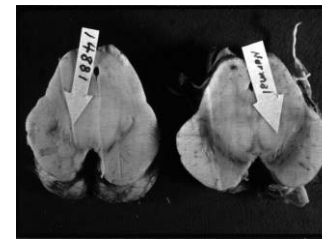


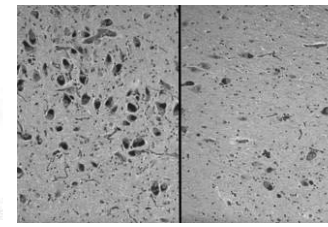
- In 1817 British physician James Parkinson published clinical descriptions of 6 patients with a syndrome of similar symptoms that he called “the shaking palsy”.
- In the 1870s the eminent French neurologist Charcot observed similar cases, and renamed the disorder “Parkinson’s disease”.
- There was little understanding of the biologic basis of the condition until the early 20th century.

Understanding Parkinson disease:

The first major breakthrough came in the early 1900s when pathologists discovered that PD patients had fewer pigmented nerve cells in an area of the midbrain called the “substantia nigra”



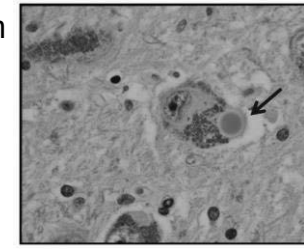




What is a **“Lewy Body”** ?

In 1913 Dr. F. Lewy was studying autopsy specimens under the microscope and observed:

- Eosinophilic inclusions in the cytoplasm of neurons in the substantia nigra of people who had Parkinson disease
  (these were eventually named “Lewy bodies”)



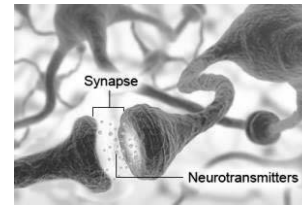
The specific pathologic hallmarks of Parkinson disease were eventually determined to be:

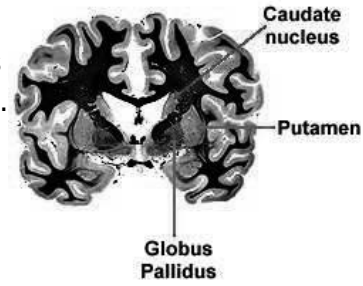
- Loss of pigmented neurons in the substantia nigra
- the presence of “Lewy bodies”

but how this was related to symptoms of PD was not appreciated until the 1960s

Neurotransmitter research: discovering the role of <u>dopamine</u> in the brain

In 1959 Dr. Carlsson performed experiments that led to the discovery that **dopamine** is a **neurotransmitter** in the brain, and that it was highly concentrated in the "**striatum"** (caudate and putamen) which was quite different from the distribution of other neurotransmitters such as serotonin and norepinephrine.

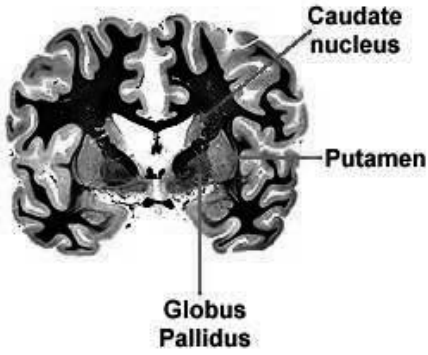




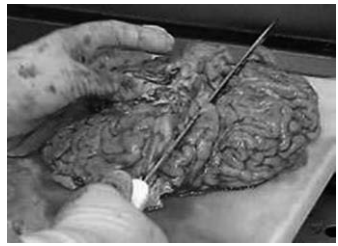
A major function of the striatum is to **"facilitate complex sequences of movements"**

(much as the conductor facilitates the harmonious music from an orchestra)

It was apparent that the striatum was not performing its function well in persons with Parkinson disease.



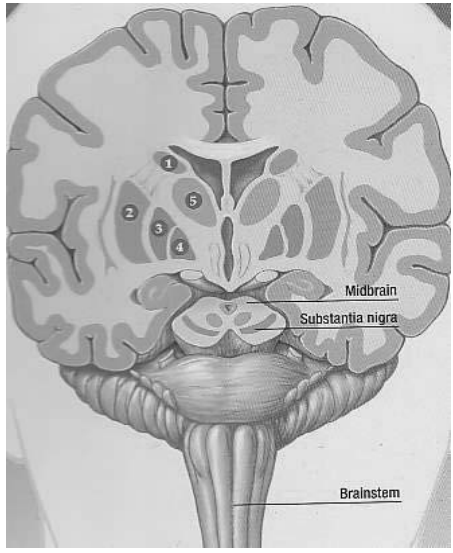
Post-mortem neurochemistry of PD

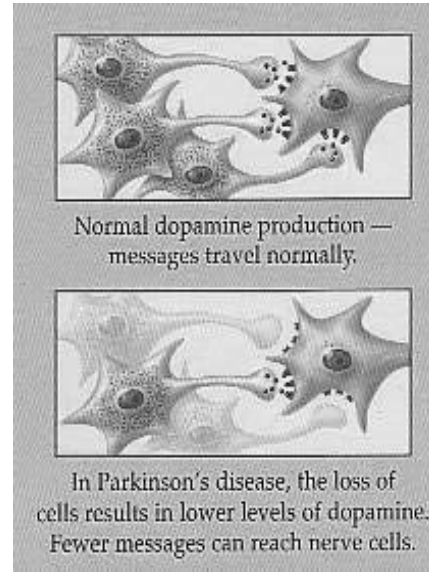


- In 1960, studying neurochemistry in autopsy specimens, Dr. Hornykiewicz found **severe depletion of dopamine in the striatum** in **PD patients**, but **not** in persons with Huntington's disease or other neurologic disorders.
- He postulated that there must be a pathway between the subtantia nigra and striatum, and speculated that the loss of dopamine in the striatum might correlate with the severity of the motor symptoms in PD. (he was quite right)

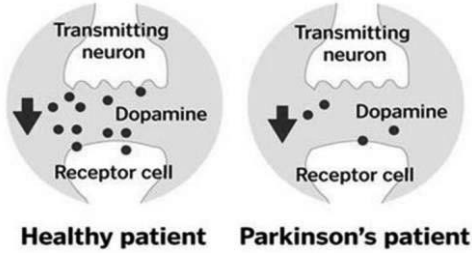
The model of PD in the late 1960s :

"midbrain nerve cells that produce dopamine degenerate in Parkinson disease":





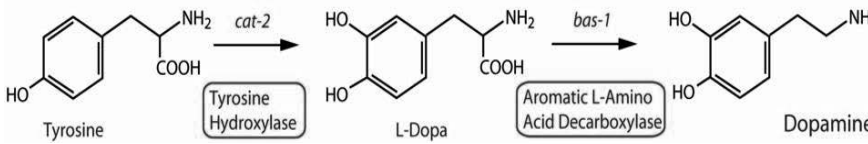
Role of dopamine in facilitating movement



Healthy patient **Parkinson's patient**

- Dopaminergic modulation of the striatum is mainly "tonic": it is not tightly linked to specific motor events
  (in simplistic terms, a steady supply of dopamine keeps the motor system "en garde", "in tune", and ready to act)
- When dopaminergic tone in this circuit is reduced by >50% voluntary movements lose amplitude and speed, and spontaneous movements are attenuated:
  "parkinsonian" motor symptoms appear!

How does the brain synthesize dopamine ?



- The amino acid **tyrosine** (which is very prevalent in the diet, but can also be synthesized in the absence of dietary sources)
  is hydroxylated to **levodopa.**
- **Levodopa** (for which there are few dietary sources)
  is decarboxylated to **dopamine.**

Tyrosine hydoxylase is the "rate-limiting enzyme" in the synthesis of L-DOPA, dopamine, and other catecholamines.

DOPA decarboxylase is not "saturable": more dopamine will be synthesized if more levodopa is present.

Could anything be done to help?

L-dopa (levodopa) in the treatment of Parkinson disease:

- L-dopa was shown to be effective in treating the motor symptoms of Parkinson disease

  George Cotzias et. al.

  NEJM 1969; 280: 337-345

- An “amazing breakthrough”: this was the first effective treatment for a neurodegenerative disease previously thought to be “untreatable” and “hopeless”

Dr. Oliver Sachs in his book “Awakenings” about early trials of levodopa referred to the medication as *“resurrectamine”.*

Levodopa in Parkinson disease:

- Dr. Cotzias was not the first to try dopa in PD, but he was the most persistent, and the first to convincingly demonstrate unequivocal benefit.
- He administered levodopa orally to a group of hospitalized PD patients, slowly and gradually increasing the doses to reduce side effects.
- Oral levodopa was not well tolerated: dopa carboxylase in the GI tract converted most of the levodopa to dopamine, which caused severe nausea and other side effects.
- However, at very high oral doses (thousands of mg), enough levodopa ultimately entered the brain to induce CNS dopamine synthesis.
- There was dramatic improvement in the motor symptoms of Parkinson disease!

Role of carbidopa in addition to levodopa in PD

Levodopa given alone is not well tolerated.

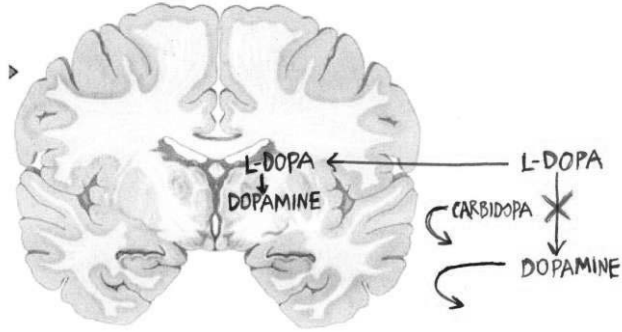
Carbidopa inhibits "dopa decarboxylase" peripherally, but does not cross the blood brain barrier, and thereby does not inhibit dopa decarboxylase in the brain.

Combining carbidopa with levodopa:

- Reduces "peripheral" dopamine synthesis (dramatically decreasing levodopa induced nausea and other side effects)
- Improves the half-life and bioavailability of oral levodopa so that more will enter the brain to enhance dopamine synthesis

(in Europe, a similar dopa decarboxylase inhibitor, benzaseride, is used in combination with levodopa rather than carbidopa)

How does carbidopa/levodopa work?



The carbidopa blocks intestinal dopa decarboxylase but does not enter the CNS: thus it prevents the systemic side effects of dopamine and allows more levodopa to enter the CNS

carbidopa/levodopa was marketed in1971 as **sinemet**:

"*sin*" (*sans*) = without "*emet*" (*emesis*) = vomiting

Soon after the introduction of levodopa, **dopamine receptor agonists** were developed

"dopamine receptor agonists":

bromocriptine and pergolide (ergot derivatives) were the earliest dopamine agonists, but these medications are no longer used due to fibrotic complications

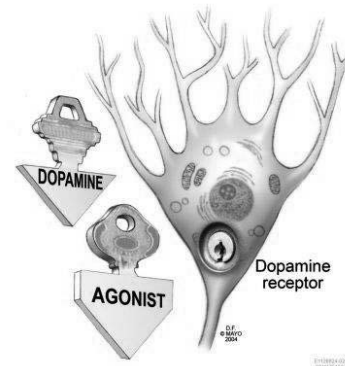
Current dopamine agonists commonly used to treat Parkinson disease:

ropinirole

pramipexole

rotigotine transdermal patch

These medications directly stimulate dopamine receptors without actually inducing dopamine synthesis.



There was a controversy regarding which medication should recommended for the initial treatment of PD:

carbidopa / levodopa or a **dopamine agonist ?**

The jury is in, and the verdict is:

carbidopa/levodopa !

"the differences in favor of initial levodopa treatment are significant and persistent"

Lancet 2014; 384: 1196-1205

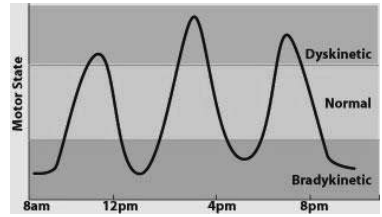
Initial therapy of Parkinson disease:
dopamine agonist vs carbidopa/levodopa ?

After years of levodopa treatment:

- Patients develop fluctuations in their response to levodopa

and

- Patients on levodopa often develop "dyskinesias"



These observations have been used as rationale for using dopamine agonists as initial therapy in PD, and delaying levodopa.

However,

this strategy has **not** been shown to improve patient outcomes.

Misconceptions about carbidopa / levodopa

"Levodopa is toxic"

or

"Levodopa stops working after 'x' number of years"

These erroneous concepts (which are still bantered about on the internet) have made many patients fearful to take levodopa, and made some physicians reluctant to properly prescribe this medication:

What are the origins and basis for this misunderstanding?

Reality about levodopa therapy:

Levodopa is **not** "toxic" and does **not** "stop working":

However,

- Levodopa is not a "cure": as PD slowly progresses over the years, the cardinal motor symptoms gradually worsen (but continue to benefit greatly from treatment with carbidopa levodopa).
- Motor symptoms **not** due to lack of dopamine (such as "freezing gait", retropulsion, dysphagia) also begin to appear in many cases, along with potentially disabling non-motor symptoms.

Delaying or avoiding levodopa treatment will not prevent these "non-dopaminergic" symptoms from eventually developing later in the course of the disease. These symptoms are not due to levodopa toxicity or because levodopa "stops working".

Levodopa: sooner or later ?


A JOURNAL OF NEUROLOGY

'Don't delay, start today': delaying levodopa does not delay motor complications

Susan H. Fox, Anthony E. Lang

Brain (2014) 137 (10): 2628-2630. **DOI:** https://doi.org/10.1093/brain/awu212
Published: 11 September 2014

Fluctuating responses to levodopa therapy largely reflect the duration and progression of the disease rather than being merely related to the duration of treatment with levodopa.

Dopamine agonists are not as effective in controlling motor symptoms, and even if used initially, every PD patient will eventually require treatment with carbidopa/levodopa:

Delaying the use of levodopa
does not prevent motor fluctuations!

Why not routinely use dopamine agonists?

Dopamine agonists are less effective in controlling motor symptoms than levodopa

Agonists have more side effects than levodopa:

- Excessive daytime sleepiness
- Nausea
- Hallucinations
- Impulse control disorders:
  - pathologic gambling
  - pathologic sexuality
- Increased risk of "freezing gait"

There is no long term prognostic advantage to the initial use of dopamine agonists for treating the motor symptoms of Parkinson disease

Lancet 2014; 384: 1196-1205

For whom might dopamine agonist therapy be considered as initial therapy for PD?

- Younger PD patients (under age 45) are at increased risk for developing severe dyskinesias on levodopa, and thus might be considered for initial therapy with dopamine agonists (which are less likely to cause dyskinesias).

However:

- Dopamine agonists are less effective in controlling motor symptoms, and all patients eventually require carbidopa/levodopa therapy.

Caution! If using a dopamine agonist you must warn that

- Dopamine agonists have been associated with an increased risk of **"sleep attacks"** (that could lead to motor vehicle accidents), hallucinations, and serious **"impulse control disorders"**

Caution when using dopamine agonists !

- All patients on dopamine agonists must be frequently screened for "impulse control disorders" (ICDs):
  - uncontrollable gambling
  - hypersexuality
  - pathologic spending

(spouses and care-partners must also be educated about these potential side effects and regularly queried, as patients frequently will deny, conceal, or minimize abnormal behaviors)

- ICDs occur in over 15% of patients receiving dopamine agonists, and may lead to serious adverse legal and psycho-social consequences.
- Levodopa mono-therapy is not associated with a significant increased risk of impulse control disorders

In summary:

Levodopa is not a "cure" for Parkinson disease and does not prevent gradual decline in motor function, but it does not "stop working".

- Many later stage PD symptoms

(such as dysphagia, dysphonia, retropulsion, "freezing gait", cognitive decline)

are not caused by lack of dopamine, and might occur whether levodopa is used early or is delayed.

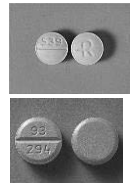
- "Motor fluctuations" are not prevented by delaying levodopa treatment.

  Delaying levodopa treatment when motor symptoms are significant is illogical.

  You can't save the best for later.

Many carbidopa/levodopa doses are available

- 10/100
- 25/100
- 25/250
- CR 25/100
- CR 50/200
- ER 23.75/95 (rytary)
- ER 36.25/145 (rytary)
- ER 48.75/195 (rytary)
- ER 62.25/245 (rytary)

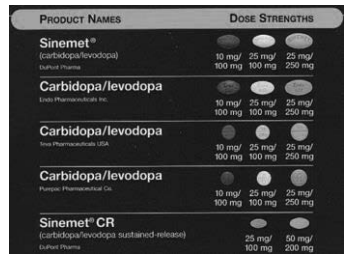


One size does not fit all !

Initial therapy is usually with ½ tablet of the 25/100 strength three times/day before meals. The dose is slowly titrated upward until you find the dose that both "works" and is well tolerated.

Patients may require as little as 150mg of levodopa/day to over 1000mg/day to optimally control their motor symptoms.

How to initiate carbidopa/levodopa: start with the 25/100 strength



Why start with 25/100 rather than 10/100?

75 to 100mg (or more) of carbidopa is needed to inhibit peripheral dopa decarboxylase:

The 25/100 strength (not 10/100) will likely achieve adequate amounts of carbidopa to block the "peripheral" conversion of levodopa to dopamine, thereby reducing nausea and making more levodopa available to enter the brain where it is needed.

Typical schedule for initiating carbidopa/levodopa

Use carbidopa/levodopa 25/100

Week 1 ½ three times/day with meals

Week 2 1 three times/day with meals

Week 3 1½ three times/day with meals

(and higher as necessary and as tolerated)

- Assess response and side effects
- Continue to titrate dose upward (or downward) as necessary to control target symptoms
- Levodopa is best absorbed on an empty stomach, but for the first few weeks when initiating therapy it might be wise to give the medication with food to prevent nausea
- If nausea is not a problem, instruct the patient to take the medication on an empty stomach >30 minutes before meals

Initiating carbidopa/levodopa

The response is variable among PD patients, and there is a wide range of effective doses:

"One size does NOT fit all"

Doses must be titrated according to improvement of the "target symptom"
(e.g. rigidity, bradykinesia, writing, gait)
and adverse effects –

Side effects such as nausea often subside if starting with very low doses and with slower titration.

Tremor is not always an ideal "target symptom":

- tremor may not respond as robustly to medication as do the other motor symptoms
- tremor is exacerbated by stress and anxiety.
- patients whose tremor is controlled 90% of the time often focus on the 10% when it is not controlled

The “do’s” and “don’ts” of treating Parkinson disease

Do not over-medicate patients!

- Used divided doses of medication, and find the lowest dose that controls the target symptoms.
- Over-medication can trigger serious side effects:
  - Dyskinesias
  - Hallucinations
  - Psychosis
  - Somnolence
  - Dopamine addiction

The “do’s” and “don’ts” of treating Parkinson disease

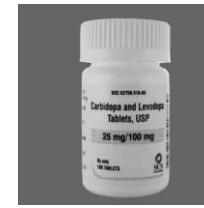
Do not under-medicate patients!

- Under-medication leads to increased disability and a greater risk of falling.
- Doses and time intervals between doses should be individualized and titrated according to the patient’s response.
- Do not use more than the lowest dose needed to control motor symptoms, but there is no reason to arbitrarily restrict the dose of carbidopa/levodopa.
- Educate your patients to improve compliance.

The goal of Parkinson disease treatment: "don't play GOOD against PERFECT"

- Find the dose of carbidopa/levodopa that works best for the patient
- Arbitrarily restricting the dose has no long term benefit:

  "you cannot save the best response for later"



- Initial therapy should be with regular carbidopa/levodopa:
  there is **no evidence** that initial treatment with "controlled release" formulations or the addition of COMT inhibitors (e.g. entacapone) produces better long-term outcomes -

carbidopa/levodopa in Parkinson disease

All patients with PD improve with carbidopa/dopa therapy

Although symptoms slowly worsen over the years, clinical benefits persist over the course of the illness

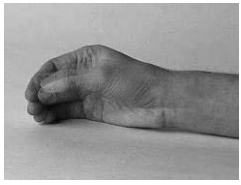
- Bradykinesia and rigidity show the best response
- Tremor is not as reliably responsive to dopaminergic therapy: some patients benefit greatly, while others, particularly those with severe tremors or uncontrolled anxiety, are less likely to note robust benefit.

Reasons for “lack of benefit” from carbidopa/levodopa:

- Symptoms are so mild that the patient does not notice improvement
- Inadequate dosing (total levodopa doses should be gradually increased to at least 1000mg daily if no improvement noted on lower doses)
- Lack of compliance
- Failure to take medication on an empty stomach
- Concurrent use of neuroleptics or other dopamine blocking drugs
- The target symptom is “non-dopaminergic”
- The patient has a another “parkinsonian disorder” rather than true Parkinson disease

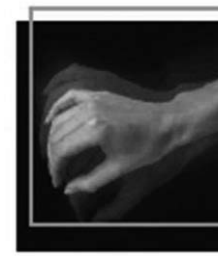
“refractory” Parkinson disease tremors

- Some PD tremors do not respond dramatically to levodopa therapy
- Higher levodopa doses (often above what is well tolerated) are sometimes required to control severe tremor
- Tremors are obtrusive, and a patient whose tremor is controlled 90% of the time may focus on the residual 10%, reporting “poor tremor control”
- Tremor wax and wane, often exacerbated by
  - stress
  - anxiety
  - fatigue



Tremor is different than other Parkinson disease motor manifestations

- Unlike rigidity and bradykinesia, severity of tremor is not directly correlated with the degree of dopamine depletion
- Other networks (serotoninergic ?) also affect tremor severity
- The progression of PD tremor may not be as evident as the gradual increase in rigidity, bradykinesia, or gait disorder that occurs over time.



Movement Disorders 2016; 31: 957-961

Anticholinergic medications in PD
(trihexyphenidyl, benztropine)

- Anticholinergic medications can reduce **rest tremor** for patients in whom dopaminergic therapy is inadequately effective.

Use with great caution, if at all!

- Unfortunately, anticholinergics are not well tolerated, particularly in the elderly, and for many patients the side effects outweigh the benefits:
  - constipation
  - urinary retention
  - dry mouth
  - memory loss / confusion
  - hallucinations
  - blurred vision

What is the goal for treating the motor symptoms in Parkinson disease?:

- To completely eliminate tremor and all other motor symptoms at all times
  (this would be nice,
  but is seldom possible)

  or
- To keep people functioning in the mainstream of life

  (a realistic goal)

Aiming for “perfection” increases the risk of over-medication and significant side effects.

Potential side effects of dopaminergic therapy

- Nausea
- Somnolence
- Orthostatic hypotension
- Dyskinesias
- *Psychiatric side effects:*
  hallucinations
  psychosis
  impulse control disorders

These side effects are generally dose related, and with the exception of dyskinesias, more prevalent in patients receiving dopamine agonists than carbidopa/levodopa.

Reducing side effects from carbidopa/levodopa

- Find the dose that "works"
- Many side effects are related to the peak blood level after each dose:

Thus if either 1 ½ or 2 tablets of carbidopa/levodopa 25/100 will control the patients motor symptoms:

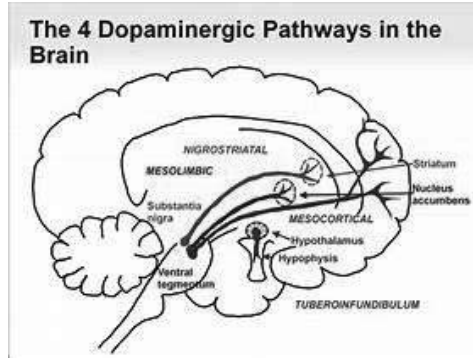
1 ½ tablets 3 or 4 times/day (doses 4 hours apart)

would be less likely to cause nausea, dyskinesia, somnolence, or orthostatic hypotension than

2 tablets 3 times/day (doses 4-6 hours apart)

Lower doses given more frequently usually cause fewer side effects than higher doses given less frequently.

Factors contributing to the side effects associated with dopaminergic medications



- Dopaminergic stimulation of the "chemo-receptor trigger zone" causes nausea.
- Stimulation of meso-limbic and meso-cortical dopaminergic pathways in susceptible patients can provoke psychiatric and behavioral side effects:
  - somnolence
  - hallucinations, psychosis,
  - impulse control disorders

Nausea, meals, and carbidopa-levodopa

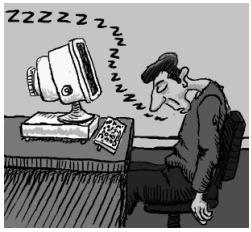
- Since meals and dietary protein delay absorption of levodopa, it is optimal to take the medication on an empty stomach (at least 30 to 45 minutes prior to meals if possible, rather than with or after meals).
- However, when initiating treatment, carbidopa levodopa may need to be taken with or after food to reduce the likelihood of queasiness, nausea, and vomiting.
- As tolerance to these side effects develops over time, this precaution is unnecessary, and levodopa should then be taken on an empty stomach.

Management of persistent nausea due to carbidopa/levodopa

- Use smaller doses of levodopa (this may not be possible if motor symptoms worsen as the dose is decreased).
- Administer carbidopa/ levodopa with food (preferably a cracker or other non-protein containing food).
- Administer additional carbidopa (marketed in the US as Iodosyn, but unfortunately is quite expensive).
- Add domperidone (an effective anti-emetic that does not aggravate parkinsonian motor symptoms, but has potential side effects on cardiac rhythm and is not available in US).
- Trimethobenzamide or ondansetron may help if domperidone is not available or contraindicated.
- Do <u>not</u> use prochlorperazine or metoclopramide! (these medications are dopamine blockers that are likely to worsen PD motor symptoms)

Excessive daytime sleepiness due to dopaminergic medications

Sleepiness is more likely in patients receiving dopamine agonists, but also problematic for some patients treated with carbidopa/levodopa.

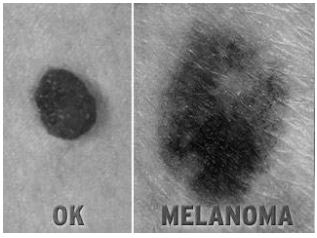


If this is a problem:

- Give smaller levodopa doses during the day and a larger dose at bedtime (the bedtime dose could capture the "long duration levodopa response", improving daytime motor function in early PD).
- Evaluate for other causes of "excessive daytime sleepiness".
- If severe, consider using a "stimulant" to reduce daytime sleepiness:

  caffeine (strong cup of coffee in morning)
  modafinil or armodafinil
  methylphenidate

Melanoma, levodopa, and Parkinson disease



- Persons with Parkinson disease have nearly twice the risk of **malignant melanoma** as the general public
- Periodic skin surveillance is appropriate for all PD patients
- It was feared that levodopa (which is a precursor of melanin) might trigger or stimulate the growth of melanomas.

Fortunately, studies have shown this not to be the case, and carbidopa levodopa can be used safely in patients PD with a prior history of melanoma.

LIMITATIONS and COMPLICATIONS of TREATMENT of the motor symptoms of PD

Unfortunately, our current treatments for PD are an incomplete miracle, and do not stop the gradual progression of the disease. There are many potential complications of treatment as well as symptoms that do not respond well to medication.

Parkinson disease is now recognized as

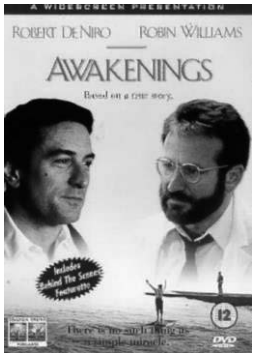
- A multisystem disorder
  (not just a “movement disorder”, but important “non-motor” problems also affect most PD patients)
- A disorder with multi-neurotransmitter dysfunction (not just dopamine deficiency)
- A very heterogeneous disorder
  (symptoms vary considerably from patient to patient)
- A disorder with many “causes”

Management issues:

Treatment must be individualized:

“one size does not fit all”

The “levodopa miracle”: what might eventually go wrong ?



- Side effects of treatment
  - fluctuating responses
  - dyskinesias
  - behavioral and psychiatric side effects
- Non-dopaminergic motor symptoms
  - dysphagia, dysphonia
  - “freezing gait”
  - retropulsion / falls
- Important “non-motor” problems
  - cognitive impairment
  - psychiatric and behavioral disorders
  - dysautonomia
  - sleep disorders

The movie “Awakenings”, based on the book by Dr. Oliver Sacks, is a powerful portrayal of the limitations encountered when levodopa was introduced and administered to a group of patients with longstanding “post-encephalitic parkinsonism”.

Many patients experience a “honeymoon period” in Parkinson disease

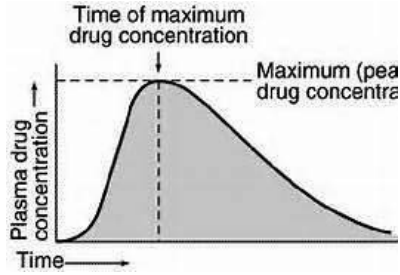
For the first several years of carbidopa/levodopa treatment

- “Dramatic benefit”
- More energetic
- Less stiffness
- Less slowness
- Imprecise timing of medication or missing doses does not adversely affect symptoms

but for some patients

- Tremor not helped to same extent as other symptoms

Pharmacokinetics of carbidopa/levodopa



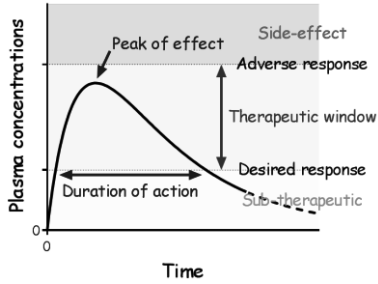
- Doses taken on an empty stomach achieve a peak plasma level in 30-45 minutes.
- Plasma levels drop to baseline in ~3 hours.
- Higher doses result in higher peak plasma levels, but do not last appreciably longer than lower doses.

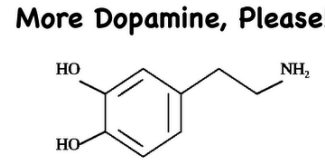
Pharmacodynamics of carbidopa/levodopa

“Long duration response”:

- During the first years of PD the clinical responses to levodopa are stable and not prone to fluctuation.
- Patients can be late or even miss doses without noticing a change in motor symptoms.
- Despite the short plasma half-life of carbidopa/levodopa, if a patient with early PD discontinues the medication it might take a week or more for symptoms to decline to baseline.

Pharmacodynamics of carbidopa/levodopa



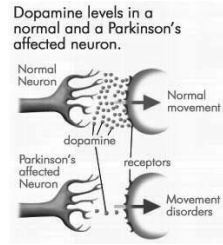


"**Short duration response**":

- As the disease progresses the "long duration response" gradually declines.
- Levodopa still "works", but the benefits wax and wane, often becoming time-locked to each dose:

Patients note improvement 20-60 minutes after each dose, only to see the effect decline (e.g. increased stiffness, slowness, shuffling gait, or tremor) after several hours.

Pharmacodynamics of levodopa: what happens to the "long duration response"?



- The "short duration response" becomes apparent when the loss of dopaminergic neurons reaches a critical threshold, resulting in diminished buffering capacity to compensate for fluctuating levodopa levels.
- Other brain cells (serotoninergic neurons and glia) might become the principle sites of levodopa uptake. These cells lack essential mechanisms for modulating dopamine concentrations.
- Dopamine release may be distant from receptors, requiring diffusion, and is unregulated by reuptake mechanisms.

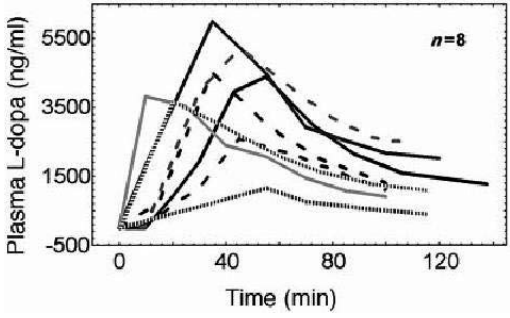
“wearing off” of levodopa effect

The earliest manifestations of fluctuating response to treatment in PD are:

- Worsening stiffness, slowness, or tremor at the end of each dose
- Return of symptoms in the middle of the night
- Early morning rigidity, tremor, bradykinesia, or dystonia
- Symptoms improve about 30 minutes after taking the next dose

At each visit, inquire whether your patients are experiencing these symptoms!

Re-timing carbidopa/levodopa doses is the first step in reducing motor fluctuations

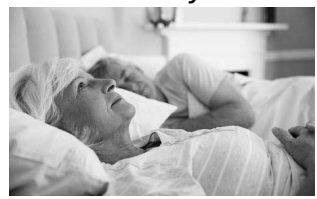


Larger carbidopa/levodopa doses do not last significantly longer (but will raise the peak blood levels, increasing the potential for dopaminergic side effects such as dyskinesias or hallucinations)

1. Find the lowest dose that “works”,
2. Determine the duration of benefit, and
3. Take the carbidopa/levodopa doses at more frequent time intervals (around the clock if necessary)

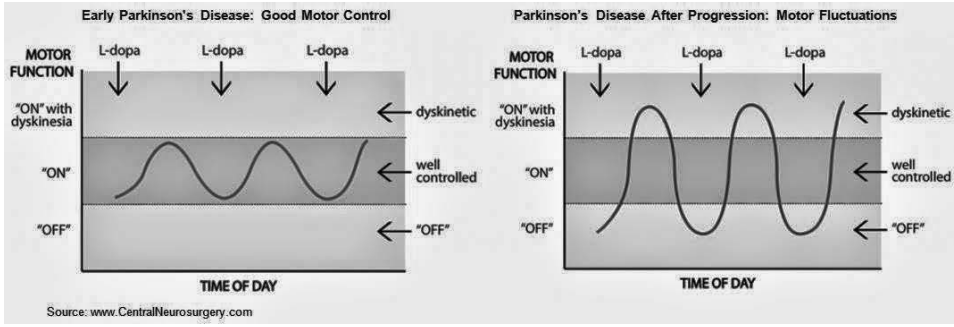
Treating “end of dose wearing off”

- Adding a COMT inhibitor or MAOb inhibitor are alternative approaches that might prolong the levodopa effect, but often the easiest and most effective approach is to simply move the carbidopa/levodopa doses closer together:
  e.g. 4 or 5 doses/day taken every 4 hours
  instead of 3 doses/day 5-6 hours apart



- Some patients might require bedtime doses or doses upon awakening in the middle of the night to prevent “wearing off” that can disrupt sleep or cause early morning bradykinesia and painful dystonia

Fluctuations in response to levodopa therapy become more notable after many years of treatment:
dyskinesias and **“off” periods**



Dyskinesia: involuntary movements as a side effect of levodopa therapy

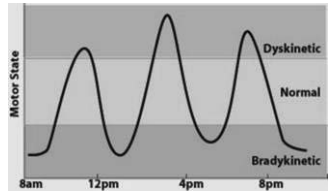
Dyskinesias are typically characterized by

- Involuntary choreiform “dancing” movements of the limbs, or trunk (usually more notable on the side initially affected by PD)
- Facial grimacing

Occasionally:

- Ballismus (flinging, flailing movements of limbs)
- Dystonia (painful cramps or abnormal posture of toes, hand)
- Bruxism (grinding teeth, jaws)
- (rarely) respiratory muscles (may cause shortness of breath)

Dyskinesia in Parkinson disease



- Medication induced choreiform movements: usually a seen “**peak dose**” (30 minutes after a dose of carbidopa / levodopa is taken)

  or “**diphasic”** (at the beginning and end of levodopa dosing period)
- The involuntary dyskinetic movements are usually more prominent on side of the body initially affected by the PD
- Like tremor, dyskinesias are often exacerbated by stress or anxiety (e.g. when speaking in public)

Impact of dyskinesias in Parkinson disease

- The patient may be relatively unaware of the involuntary movements.
- Even when noted, dyskinesia is not necessarily unpleasant or bothersome to the patient.
- Family members often notice the movements, and may find them more distressing than the patient (particularly if there is grimacing or other involuntary facial or head movements).
- **Most patients generally prefer being "dyskinetic" rather than bradykinetic, immobile, or rigid.**
- However, when severe, dyskinesias can be embarrassing and disabling.

Management of dyskinesias

- No treatment is needed in milder cases (patients prefer to be dyskinetic rather than bradykinetic or rigid)

However, if dyskinesias are troubling, treatment is needed:

- Reducing each levodopa dose should diminish dyskinesia:

For example:

If the patient is currently experiencing troubling dyskinesias while on

carbidopa/levodopa 25/100 2 tablets every 4 hours

you might try reducing the dose to

carbidopa/levodopa 1 ¾ or 1 ½ tablets every 4 hours

Management of dyskinesias

Decreasing the levodopa dose may not be tolerated if parkinsonian motor symptoms subsequently worsen:

In this case options include:

- Continue the original levodopa dose and add amantadine which will reduce dyskinesias

or

- Continue lower doses of levodopa and add a dopamine agonist to improve motor function (dopamine agonists generally do not cause or exacerbate dyskinesias)

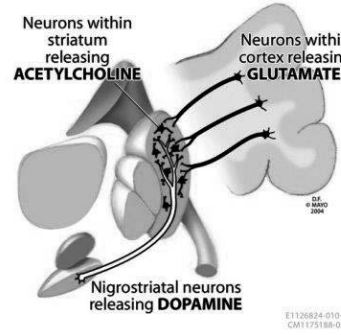
How does amantadine work?

Amantadine was originally introduced in the 1960s as an anti-viral agent but was also found to have beneficial effects in Parkinson disease.

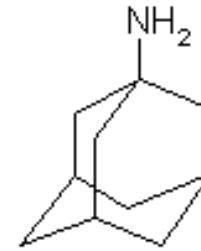
The mechanism of action is uncertain

- Mild anticholinergic effects
- Partially blocks glutamate NMDA receptors (which are up-regulated in PD patients with dyskinesia)

Amantadine can partially reduce dyskinesias without necessarily requiring a decrease the original carbidopa levodopa dose.

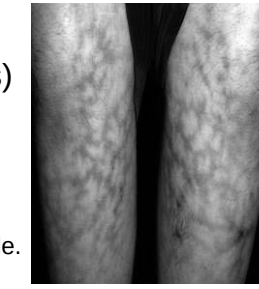


Amantadine



Helpful in reducing dyskinesias in patients treated with levodopa, but:

- Can cause anticholinergic side-effects
- Can trigger delirium and hallucinations
- Use cautiously in the elderly
- May cause livedo reticularis (purplish discoloration and mottling of legs)



The usual dose is 50 -100mg twice/day but some patients might require more

An expensive sustained release amantadine is also available.

Amantadine undergoes renal clearance: therefore the dose must be decreased in patients with azotemia !

"Dyskinesia" versus "akathisia"

Akathisia (a feeling of "inner tremor" or restlessness) is common in PD but is often misdiagnosed or misinterpreted:

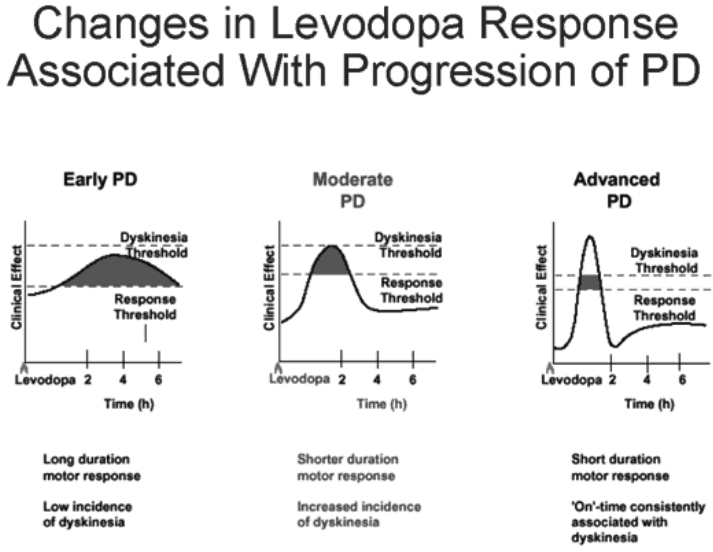
- If the patient looks "restless" (but feels relaxed), and has involuntary choreiform movements, it is dyskinesia!

  (too much dopamine)

- If the patient feels an **"inner tremor"** or feels **"restless"** or an urge to move around, but does not have tremor or chorea, it is likely **akathisia** !

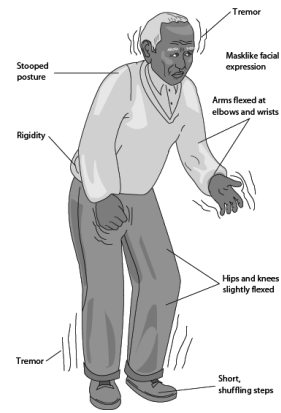
  (too little dopamine)

The "therapeutic window" narrows, and fluctuating responses to treatment may become more notable and less predictable in patients who have had PD for many years.



Patterns of "off" periods in PD:

- **Morning "off"**: increased motor symptoms upon awakening in the morning prior to the first dose of carbidopa/levodopa
- **Wearing off**: return of symptoms at the end of the dosing cycle prior to the next dose of carbidopa/levodopa
- **Delayed "on"**: a dose takes longer than expected to kick in to improve symptoms
- **"No on":** a dose fails to kick in to provide improvement in symptoms
- **Unexpected off**: a sudden and seemingly random transition from "on" to "off"



“ON” and “OFF” spells in Parkinson disease: “motor” symptoms can fluctuate dramatically

When “on”

- The patient functions reasonably well

When “off”

- Increased rigidity and /or
- Increased bradykinesia and/or
- Increased tremor and/or
- Increased pain and/or
- Increased difficulty ambulation
- Anxiety, depression and other non-motor symptoms become magnified

The difference between “on” and “off” can be dramatic and potentially devastating to the patient (and poorly understood by friends and family).

Pain in Parkinson disease

- Pain may be an early symptom of PD, but usually occurs later in the disease when the patient is **“off”**
- Pain due to PD is often **misdiagnosed** and attributed to medical or orthopedic problems
- Pain affects the side of the body most affected by PD.
- The quality of pain is often described as:

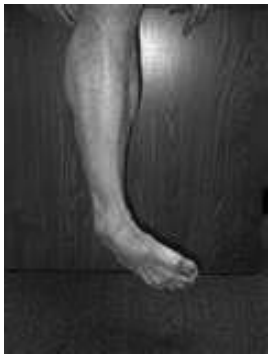
  “cramping” “tenseness”

  “stiffness” “tightness”

  “burning” “stinging”

The pain can be **SEVERE** and **DISABLING**, and may be palliated by higher levodopa doses.

Motor fluctuations:
“on” versus “off” dystonia

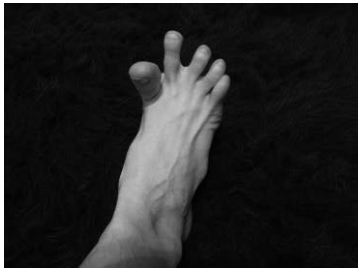


Toe curling and abnormal foot or hand postures suggest dystonia.

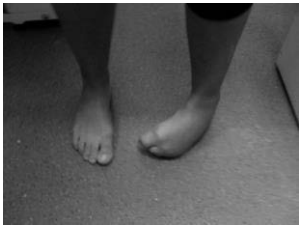
- Dystonia by itself in PD usually indicates inadequate dopamine levels in the brain (“off dystonia”)

  (try giving **more** levodopa)
- Dystonia accompanied by dyskinesia suggests dopamine excess (“dystonic dyskinesia” or “on dystonia”)

  (try giving **less** levodopa)



Botulinum neurotoxin therapy for dystonia



- Dystonia is often painful and unpleasant, and, if persistent, causes contractures.
- If changes in the timing and doses of levodopa is not helpful, administration of botulinum toxin injections by a physician with special expertise in this area can often effectively reduce dystonia in the foot, hand, neck (cervical dystonia), or eyelids (blepharospasm).
- Injections need to be repeated several times/year, as the effect of the neurotoxin often wears off 3 or 4 months after treatment.

“non-motor” fluctuations also occur and can be as troubling as the “motor” fluctuations:
Potential non-motor “off” symptoms include:

“Psychiatric”:

- Anxiety
- Panic attacks
- Altered mood / depression
- Fatigue

“Cognitive”:

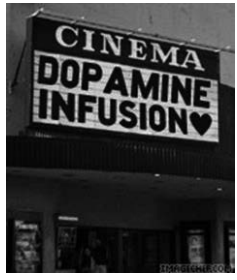
- Bradyphrenia
- Confusion
- Memory impairment
- Word finding problems

- There is often (but not always) a correlation between the timing of “motor” and “non-motor” symptom fluctuations.
- Treatments to reduce motor “off” time do not necessarily benefit the severity of non-motor off symptoms.
- Non-motor fluctuations can be very unpleasant and devastating to the patient.

Non-motor symptoms that might respond to levodopa

(non-specific fluctuating symptoms that could be due to **inadequate dopamine**)

- Anxiety and panic attacks
- Akathisia and “inner tremor”
- Restless legs
- Dysphoria and irritability
- Severe pains or cramping in limbs or abdomen
- Insomnia
- Hot flashes and diaphoresis
- Urinary urgency
- Dyspnea
- Poor concentration / bradyphrenia



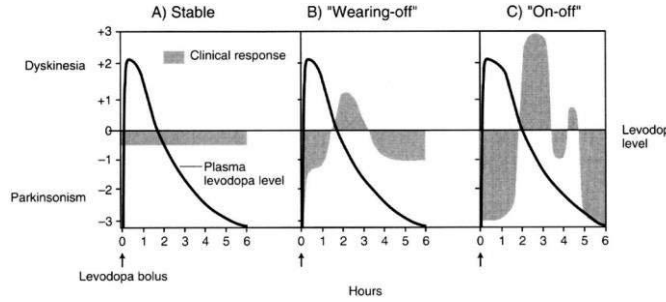
Non-motor symptoms that might respond to levodopa

(non-specific symptoms that could be due to **inadequate dopamine**)

How do you determine if the symptom is due to Parkinson disease?

- Did the symptom develop with or after the diagnosis of PD?
- Do the symptoms come and go with the levodopa dose cycles?
- Does the symptom occur during the night (when the effect of the last dose of levodopa has presumably worn off)?
- Do the symptoms abate when the patient is dyskinetic (when there is presumably excess dopamine)?

In severe cases, fluctuations may become less predictable:

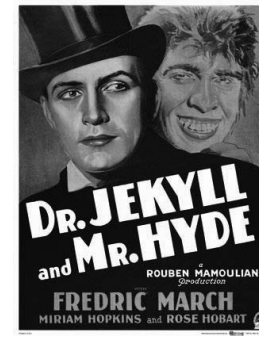


- For some patients the “off” periods are random, often unrelated to the timing of the medication.
- Emotional distress or “anticipatory anxiety” can trigger “off” spells.
- Some doses of levodopa “don’t work” (“dose failure” or “no on”) probably caused by delayed absorption.
- Some “off” periods occur very abruptly, at predictable or unpredictable times.

Coping with symptom fluctuations in PD

Fluctuating symptoms are a major source of disability:

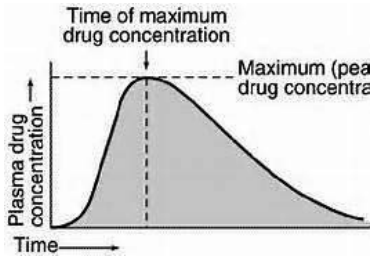
- It becomes difficult to make plans, because patients do not know if they will be “on” or “off”
- The family often does not understand the problem, and thinks the patient is “faking it” or being manipulative or lazy:

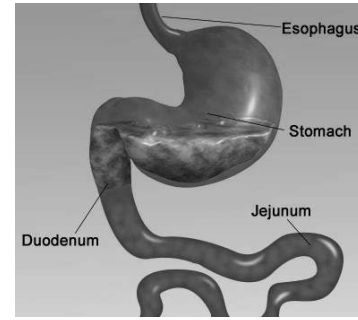


“It’s like Dr. Jekyll and Mr. Hyde. How can someone walk well at 9am and suddenly be unable to walk at 10am?”

The physician must educate the patient and family about the nature and cause of fluctuating symptoms in Parkinson disease, and review treatment options.

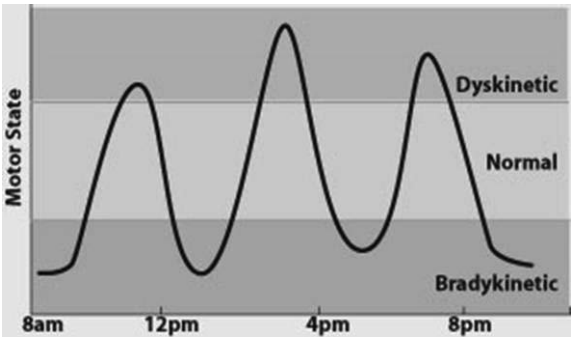
Why do symptoms fluctuate ?





- Progressive neuronal loss alters brain dopamine synthesis, and reduces the capacity to buffer fluctuating levodopa levels.
- Lack of pre-synaptic regulatory mechanisms in non-dopaminergic cells that can synthesize dopamine from levodopa.
- Short half-life of carbidopa/levodopa (2-3 hours)
- Levodopa is absorbed in the jejunum, competing with “large neutral amino acids” in the diet.
- Delayed gastric emptying / gastroparesis

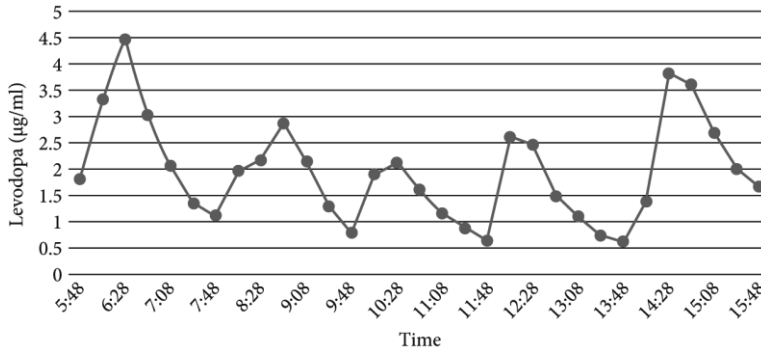
What can be done to minimize clinical "fluctuations" in response to carbidopa/levodopa therapy ?



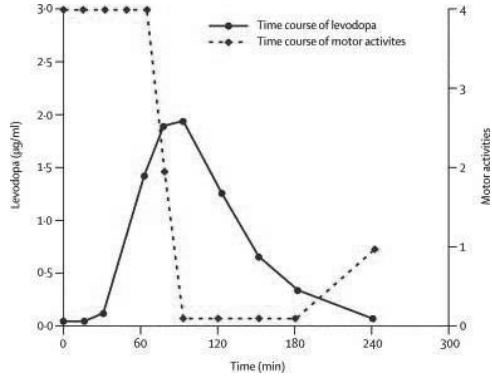
"continuous dopaminergic stimulation"

stable plasma levodopa levels should be the goal of treatment:

Unfortunately, levodopa levels will vary greatly even with very frequent oral dosing, thereby contributing to fluctuating motor and non-motor symptoms.



Optimizing levodopa to manage fluctuations:

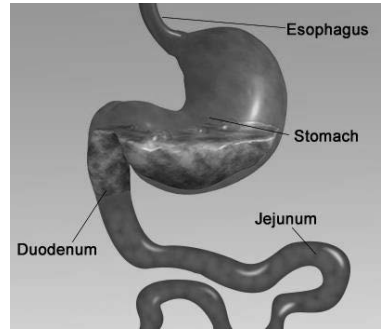


- Determine the dose that produces the best response at peak effect without significant side effects.
- Adjust the time interval between doses to match the duration of the response.

Recall that larger individual doses do **not** lengthen the duration of response, but produce higher peak blood levels that could exacerbate side effects such as dyskinesias or hallucinations.

Effect of meals and protein on levodopa levels

- Meals reduce peak plasma levodopa concentrations by approximately 25%
- Meals delay absorption of levodopa by ~30 minutes
- High protein meals reduce the therapeutic effect of levodopa: dietary large neutral amino acids compete with levodopa (which is also a large neutral amino acid) for facilitated absorption in the jejunum and for transport across the blood brain barrier
- Many PD patients have some degree of gastroparesis (delayed gastric emptying) that also contributes to erratic levodopa absorption



“protein redistribution diet” for PD

Patients with significant fluctuations may benefit from avoiding protein containing foods with breakfast and lunch:

low or no protein foods:

muffins, breads, jams, salads, fruit

high protein foods:

dairy products, fish, eggs, meat, nuts

- Protein containing foods can be consumed with dinner or at night when the patient is planning to be less active

Do all PD patients with fluctuations require a protein redistribution diet?

NO! But for best effect encourage patients to take levodopa on an empty stomach whenever possible:

- At least 30- 45 minutes before meals

  or

- About 2 hours after meals

When taken on an empty stomach before meals, levodopa should enter the brain within 15 to 45 minutes (unless there is significant gastroparesis) .

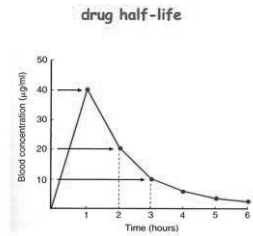
If taken about 2 hours after completion of a meal, competition from dietary amino acids should not be a factor affecting levodopa absorption.

“pearls” to optimize treatment with carbidopa/levodopa”

- Find the levodopa dose that “works”.
- Find the proper time interval between doses.
- Smaller doses given frequently have fewer side effects than larger doses less often.
- Larger doses of levodopa do not last longer than smaller doses.
- Compliance with the schedule is important.
- Levodopa is absorbed more quickly and completely on an empty stomach.
- Re-distributing dietary protein to the evening can reduce “off” time during the day.
- Bedtime and middle of night doses are helpful if PD symptoms interfere with sleep.
- Monitor closely for side effects:
  dyskinesias, hallucinations, psychosis

Longer acting carbidopa/levodopa to reduce fluctuating symptoms:

Immediate release carbidopa/levodopa has a short half life



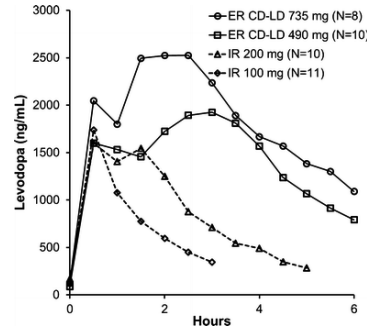
Somewhat longer acting forms of carbidopa/levodopa are available:

- carbidopa/levodopa CR (“controlled release”)
  25/100 or 50/200
- carbidopa/levodopa “extended release” (brand name rytary)
  23.75/95, 36.25/145, 48.75/195, 61.25/245

What is their role in treating Parkinson disease?

carbidopa/levodopa CR (ER) “controlled release”

- Carbidopa/levodopa CR might last 60-90 minutes longer than regular immediate release (IR) carbidopa/levodopa



However:

- Absorption of the CR formulation is more erratic than IR carb/levodopa
- Lower peak blood levels of CR may not be high enough to create an effect in some patients
- The latency to clinical response of CR may be quite delayed compared to IR
- The bioavailability is only ~70% (thus 100mg of CR is equivalent to ~70mg of regular carbidopa/levodopa)

carbidopa/levodopa CR (“controlled release”)

- For patients experiencing no “on” effect or a delayed “on” effect when taking the CR preparation, a small dose of “regular” carbidopa/levodopa can be co-administered along with the CR to provide more rapid onset of action:

For example:

carbidopa/levodopa CR 25/200 1 tablet
plus
carbidopa/levodopa 25/100 ½ tablet

can be co-administered every 4 hours

(if effective, this is a much less costly approach than the extended release carbidopa/levodopa preparation marketed as “rytary”)

If adjusting the carbidopa/levodopa dosing and time schedule is not successfully managing fluctuations:

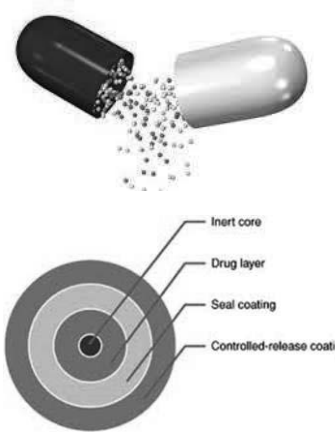
Rytary is a more effective extended release formulation than carbidopa/levodopa CR

Rytary contains carbidopa/levodopa in a 1 : 4 ratio:

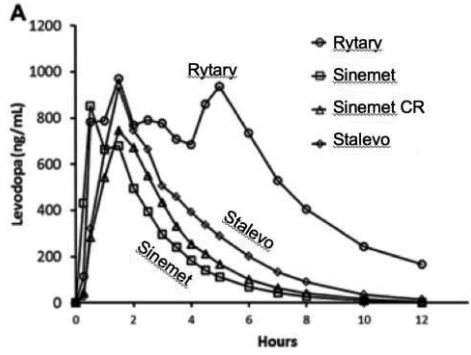
- 23.75 / 95mg
- 36.25 / 145mg
- 48.75 / 195mg
- 61.25 / 245mg

The beads in the rytary capsule are 1/3 regular carbidopa levodopa and 2/3 coated for delayed release

Doses usually given 3 to 5 times per day as needed



Rytary: longer acting carbidopa/levodopa



- The bio-availability of levodopa in rytary is lower than that of “regular” carbidopa/levodopa
- After an initial peak of levodopa 1 hour after dosing, plasma concentrations are maintained for ~ 4 to 5 hours
- Rytary can be taken with or without food, but preferably on an empty stomach, as meals can delay absorption

Converting from “**regular**” (IR) **carbidopa/levodopa** to **rytary**: the doses are **not** interchangeable!

Total ‘”regular” daily levodopa dose :	Approximate equivalent dosing of rytary capsules:
400 – 550mg/day	855mg: 3 23.75/95 tid
550 - 750mg/day	1140mg: 4 23.75/95 tid
750 – 950mg/day	1305mg: 3 36.25/145 tid
950 - 1250mg/day	1755mg: 3 48.75/195 tid
> 1250mg/day	2205-2340mg: 3 61.25/245 tid or 4 48.75/195 tid

(Rytary may be more effective in 4 or 5 smaller doses/day rather than given as 3 doses/day)

Converting from “regular” carbidopa/levodopa to “extended release” rytary:

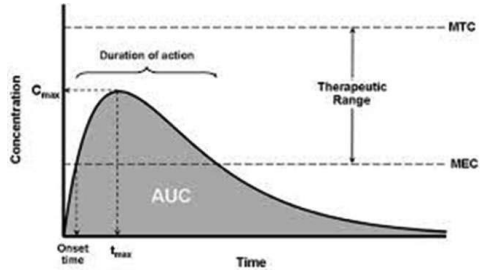
The FDA guidelines are just a starting point
In clinical practice doses must be titrated:

- ~60% need more rytary than recommended in the FDA guidelines
- ~16% require less rytary

Overall, patients with fluctuations need about twice as much levodopa in rytary than in regular carbidopa/levodopa.

Rytary is usually given in 4 or 5 daily doses about 4 ½ to 5 hours apart for Parkinson disease patients with motor fluctuations whose symptoms cannot be adequately controlled with less expensive carbidopa/levodopa regimens.

Converting from “regular” carbidopa/levodopa to rytary: **practical considerations**



The C-max of rytary is only ~ 30% of regular carbidopa/levodopa:
Thus in practice administer ~2 ½ - 3 times as much for an individual dose, but only 2/3s as often!
For example:
carbidopa/levodopa 25/100 1 ½ six (6) times per day
would be converted to
3 capsules of rytary 36.25/145 given four (4) times per day

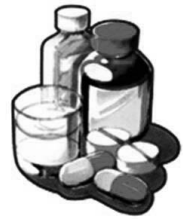
Converting from “regular” carbidopa/levodopa to rytary: **practical considerations**

- Predicting the optimal rytary dose is imprecise: titration is often necessary
- Often it is best to start by switching only the first daily carbidopa/levodopa dose to rytary, instructing the patient to resume their usual doses of regular carbidopa/levodopa about 5 hours later for the remainder of the day
- Once the optimal amount and duration of action of the morning dose is determined, the patient can be switched from carbidopa/levodopa to rytary around the clock (usually between 3 to 5 doses per day taken 4 ½ to 5 hours apart)

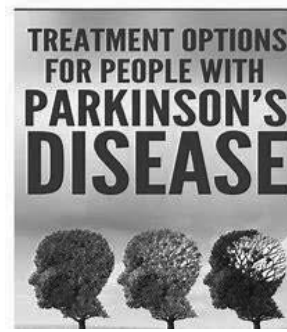
“Levodopa equivalent daily dose”
an approximate guide for comparing or converting doses of levodopa in different formulations

carbidopa/levodopa CR 25/100 is equivalent to
~ 70mg of levodopa in regular (immediate release) carbidopa/levodopa 25/100

100mg of “extended release” (rytary) is equivalent to
~ 40mg of levodopa in carbidopa/levodopa 25/100

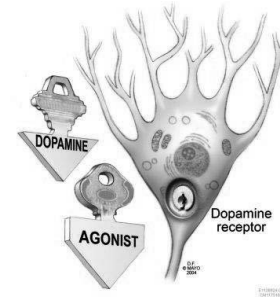


When fluctuating symptoms are not well controlled,
other medications can be helpful as adjuncts to carbidopa/levodopa:



- Dopamine agonists:
  - pramipexole
  - ropinerole
  - rotigotine patch
  - apomorphine injection
- Catechol-O-methyl transferase (COMT) inhibitors:
  - entacapone
  - tolcapone
- Monoamine oxidase type B (MAOb inhibitors)
  - selegiline
  - rasagiline
  - safinamide

Dopamine agonists (pramipexole, ropinerole, rotigotine) **for fluctuating symptoms in PD**



- Dopamine agonists have a longer half-life than carbidopa/levodopa (but are less effective than levodopa in reducing motor symptoms).
- Dopamine agonists are less likely to induce dyskinesias than levodopa.
- Adding a dopamine agonist may help improve motor symptoms when the doses of carbidopa/levodopa need to be lowered to control severe dyskinesias.
- Start with very low doses of the dopamine agonist, and slowly titrate upward.

Caution! "polypharmacy" increases the risk of psychosis and impulse control disorders !

Apomorphine injection: a rapidly acting treatment for severe "off spells"

- Apomorphine is a potent dopamine agonist (derived from morphine, but apomorphine is <u>not</u> a narcotic, and does not stimulate opioid receptors).
- Unlike other dopamine agonists, apomorphine is as effective as levodopa in alleviating the motor symptoms of PD.
- Administered by subcutaneous injection (doses must be titrated: 0.1-0.5mg)
- Rapid onset of action (usually <10 minutes) in alleviating motor symptoms, "off" period pain, and dystonia
- Therapeutic effect lasts 1-2 hours
- Doses can be repeated if necessary

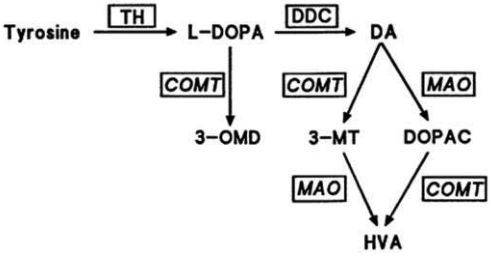
Rapidly acting treatments for severe “off spells”

The use of apomorphine is limited by

- Side effects (nausea, orthostatic BP) pretreatment with an anti-emetic such as domperidone or trimethobenzamide is necessary before using these injections.
- Very significant expense
- Injection therapies are impractical for many patients (alternative methods of delivering apomorphine are being investigated).

An inhaled powder preparation of carbidopa levodopa (Inbrija) to be used as a “rescue treatment” for severe “off spells” has recently become available. It is unclear whether this is more cost effective than merely taking a small extra dose of oral carbidopa levodopa.

“Levodopa extenders”: catechol-O-methyl transferase (COMT) inhibitors

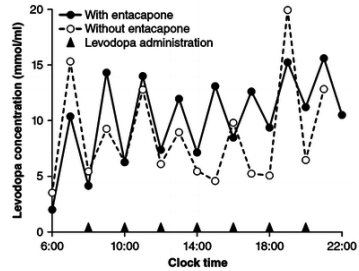


COMT inhibitor: entacapone 200mg

- Entacapone inhibits COMT peripherally (not centrally), thereby increasing the elimination half-life of levodopa.
- Combined with carbidopa/levodopa, entacapone modestly increases “on” time for some patients with fluctuating motor symptoms.
- COMT inhibitors do not prevent the development of motor fluctuations if used with carbidopa/levodopa early in the disease.

Tolcapone is more potent than entacapone as it inhibits COMT both peripherally and centrally, but is seldom used due to risk of hepatotoxicity.

“Levodopa extenders”:
catechol-O-methyl transferase (COMT) inhibitors



COMT inhibitors: entacapone 200mg

- A dose is administered with each dose of carbidopa/levodopa

Side effects:

- The modestly increased and prolonged levodopa levels caused by inhibition of COMT with can induce or exacerbate dyskinesias, hallucinations, and other dopaminergic side effects
- Nausea / diarrhea
- Discoloration of urine

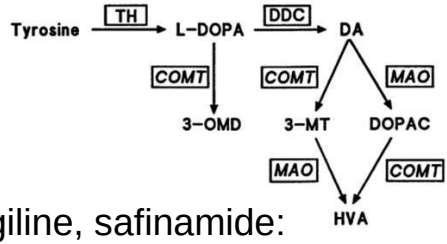
Polymorphisms in the COMT gene can increase or decrease the likelihood of benefit from treatment with entacapone.

“Levodopa equivalent daily dose”

an approximate guide for comparing or converting doses of Parkinson medications

- Rotigotine patch 6mg/day is equivalent to
  ~ 180mg of regular carbidopa/levodopa
- Ropinerole 8mg/day is equivalent to
  ~ 160mg of regular carbidopa/levodopa
- Pramipexole 2mg/day is equivalent to
  ~ 200mg of regular carbidopa/levodopa
- Carbidopa/levodopa 25/100 combined with entacapone 200mg is equivalent to
  ~ 133mg of regular carbidopa/levodopa

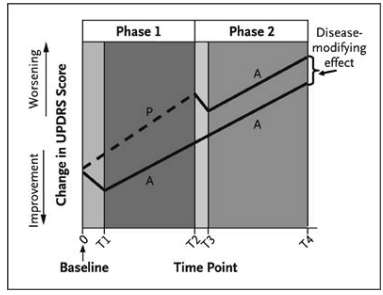
“Levodopa extenders”: monoamine oxidase type b (MAOb) inhibitors



selegiline, rasagiline, safinamide:

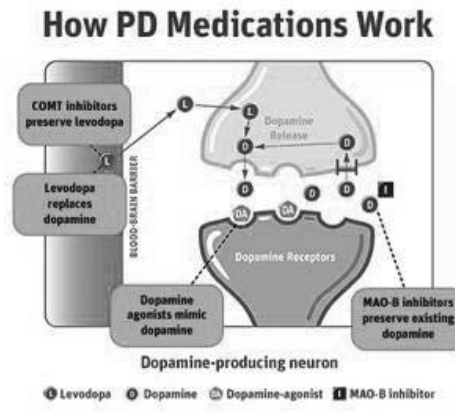
- MAOb inhibition blocks the central metabolism of dopamine, raising brain dopamine levels to some extent.
- Modest benefit for prolonging “on” time for patients with fluctuating responses to carbidopa/levodopa
- Can increase dyskinesias and other dopaminergic side effects
- In recommended doses, selective MAOb inhibition does not cause the “cheese effect” problems associated with the use of MAOa inhibitors.

MAOb inhibitors: selegiline, rasagiline, safinamide



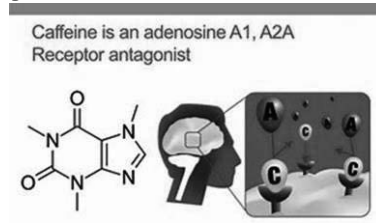
- Selegiline and rasagiline were initially studied for potential “neuroprotective” effects in slowing progression of PD. (Unfortunately, they do not have significant disease modifying activity, although secondary analysis of earlier studies raises the possibility of less long term clinical decline in patients who have had greater duration treatment with MAOb inhibitors.)
- Modest symptomatic effects on PD when used as monotherapy
- MAOb inhibitors will modestly prolong and enhance the effect of carbidopa/levodopa in patients with “fluctuations”.

Limitations of MAOb and COMT inhibitors



In summary:
adding MAOb and COMT inhibitors to carbidopa/levodopa modestly enhances and prolongs the beneficial effects of levodopa on motor function for some patients, but might also trigger or potentiate adverse effects of dopaminergic therapy:
dyskinesias, hallucinations, psychosis

Adenosine A2A receptor antagonists: istradefylline reduces "off" time in PD



- Adenosine receptor stimulation inhibits dopamine release.
- The adenosine A2A receptor antagonist istradefylline (20mg to 40mg per day) enhances dopamine release and modestly reduced daily "off" time and increased "on" time in 3 of 4 clinical trials. (The one "negative" study had a very large "placebo effect".)
- The most common side effect is increased dyskinesia
- The maximum recommended dose in patients also being treated with CYP3A4 inhibitors is 20mg/day.
- In 2019 FDA approved istradefylline for treating fluctuations: it is quite costly
- Caffeine and theophylline are also adenosine receptor antagonists.

Complex medication schedules might be needed for PD patients with significant "fluctuations"

for example:

	7am	10am	1pm	4pm	7pm	10pm	1am	4am
Carbidopa-levodopa 25/100		1 ½		1 ½	1 ½	1	1	(1) (1)
Carbidopa-levodopa ER 25/100							1	
Ropinerole 4mg			1		1		1	
Entacapone 200mg			1	1	1	1	1	1
Selegiline 5mg			1		1			
Amantadine 100mg			1			1		

Extended release carbidopa/levodopa (rytary) might decrease the amount of polypharmacy, but the high cost of this medication limits its availability for all patients.

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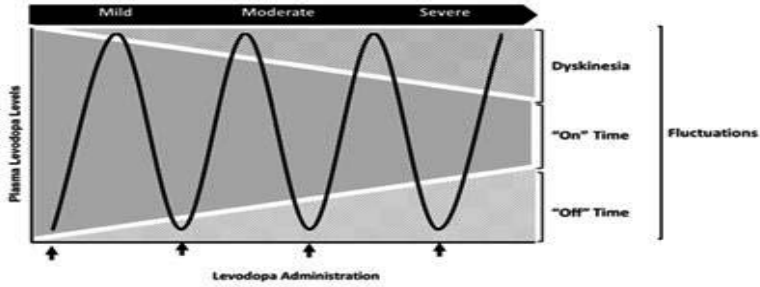


Adjusting the timing and doses of levodopa is helpful but COMPLIANCE is CRUCIAL !

- Patients with fluctuations must adhere to a very reliable time schedule for dosing of carbidopa levodopa.
- Doses should be taken on an empty stomach when possible in all cases, and dietary protein redistributed to the evening for some patients.
- Use of a "timer" (e.g. on a "smart phone") helps improve compliance.
- The physician's recommendations will not be helpful if the patient is unreliable or not compliant !

The “pill question”

Patients with Parkinson disease should be able to name their medications, doses, and time schedule:

- Inaccurate reporting suggests non-compliance or confusion
- Inaccurate reporting suggests that the patient cannot take their medications reliably or safely on their own, and therefore requires some supervision.

Patients should know their medications!

Caution: risk of over-medication !

Aggressive adjustment of levodopa and use of polypharmacy to eliminate “off” time can result in over-medication with serious side effects:

- Intolerable dyskinesias
- Hallucinations
- Psychosis
- Impulse control disorders
- “Dopamine addiction”

(these topics are reviewed later in this primer in the sections on behavioral and psychiatric problems in PD)

When treating Parkinson disease we often have to settle for “good” rather than “perfect” in order to avoid over-medication.

Correct dosing: **“on time, every time”** is **critical** for treating patients with fluctuating symptoms

- This is challenging but can be done at home: recommend using timers, or other reminders (engaging the assistance of care-partners if necessary)

However:

- When patients are hospitalized or in other institutions, patients are at increased risk on not receiving their medications “on time” to prevent motor or non-motor fluctuations
- Medication errors are common when patients are institutionalized.

Clinical problems in the hospitalized Parkinson disease patient :

Hospitalization on medical or surgical wards or rehabilitation units that have little familiarity with the management of PD often results in serious complications.

Spectrum of common issues:

- Incorrect timing of administration of the patient’s PD medications
- Incorrect dosing of PD medications
- Increased risk of delirium in hospital
- Administration of contraindicated medications (e.g. neuroleptics)
- Complications of immobilization
- Increased length of stay

Physicians and families must be proactive in providing lists and timing schedules for all medications. Instruct the family to notify you immediately if hospitalization is required, so that you can confer with (and educate) the treating physicians about the patient.

Averting clinical problems in the hospitalized Parkinson disease patient :

- Patients should bring their PD medications with them to the hospital (some medications may be “non-formulary” and not immediately available)
- An accurate list of the doses and timing of medications should be provided to the staff caring for the patient
- The importance of good communication between the physician treating the patient’s PD and the hospital staff cannot be over-estimated
- The physicians, nurses, and pharmacy must be educated regarding “fluctuations” and why **precise timing** of medications is important to prevent these problems:

Doses must be given **ON TIME EVERY TIME!**

(the common hospital policy of allowing a 1 or 2 hour time window for medication administration is NOT appropriate for PD patients who are experiencing “motor” or “non-motor” fluctuations)

Sudden deterioration of parkinsonism

PD is a slowly progressive disorder: a sudden dramatic worsening of tremor or other motor symptoms could reflect an unusually severe “off” spell, but often suggests that something else might be going on:

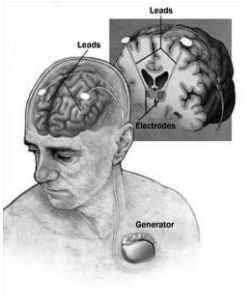
- Missed doses of PD medication
- Over-medication
- Infection
- Toxic / metabolic disorders
- Administration of dopamine blocking medications
- Stroke or subdural hematoma

PD patients are also at increased risk of altered mental status and delirium in the setting of intercurrent medical illnesses or metabolic disorders.

SURGICAL APPROACHES to TREATING the MOTOR SYMPTOMS of PD

These “advanced therapies” for Parkinson disease can successfully palliate symptoms in properly selected patients whose fluctuating symptoms or severe tremors are not adequately controlled with oral medications.

When adjusting oral therapies does not provide adequate control, surgical therapies can reduce motor fluctuations



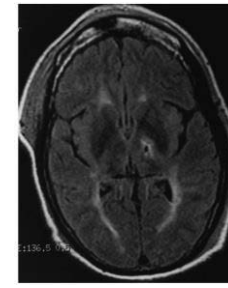
- “deep brain stimulation” (DBS)

  and

- continuous carbidopa/levodopa gel infusion into the jejunum (duopa)

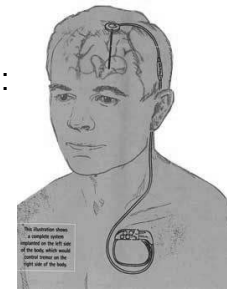
have become important therapeutic options that improve the quality of life for carefully selected patients.

“Functional Neurosurgery”
the role of brain surgery in Parkinson disease

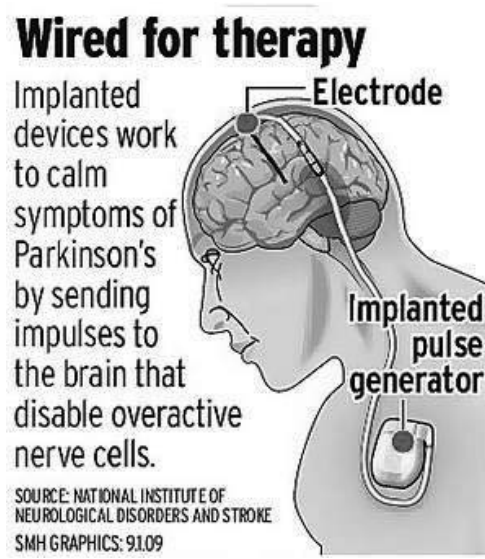


“ablation” versus **“stimulation”**:

- “lesioning” the brain (ablation) with thalamotomy or pallidotomy:
  irreversible
  damages an already impaired brain
  (“lesioning” is seldom recommended since the introduction of DBS surgery)
- Advantages of “high frequency electrical stimulation” (“deep brain stimulation” - DBS):
  reversibility
  little or no damage
  adaptability / fine tuning



Basic principle of “deep brain stimulation”



Who is an appropriate candidate for "**deep brain stimulation surgery**"?

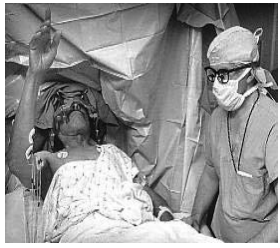
Patients who show good benefit from levodopa but nevertheless have

- *fluctuating responses* or
- *severe dykinesias* or
- *refractory tremors*

are appropriate candidates for DBS.

Patients with symptoms that do not benefit from levodopa therapy (other than severe tremor that is not responding to levodopa) are **not** appropriate candidates for DBS.

DBS surgery for Parkinson disease



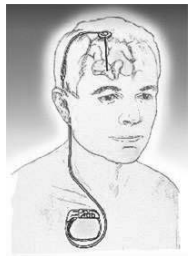


Figure 3. Deep brain stimulation (DBS) system with DBS electrode connected to pulse generator implanted in upper chest.

"<u>Ideal candidates</u>":

- Typical PD
- No significant psychiatric or cognitive problems
- Good general health with no surgical contraindications
- Good response to levodopa

but has

- Refractory tremor or
- Refractory dyskinesias or
- Poorly controlled "on / off" motor fluctuations

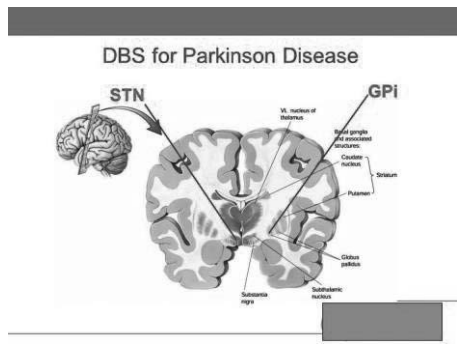
DBS surgery for Parkinson's disease

"<u>Poor candidates</u>":

- Atypical parkinsonism
- Poor response to levodopa
- Major "non-dopaminergic" problems
- Memory problems or dementia
- Severe depression or apathy
- Severe medical problems
- Unrealistic expectations

Proper patient selection is of paramount importance for ensuring meaningful benefit from DBS surgery.

DBS has become the "gold standard" for the surgical treatment of PD



Targets for DBS:

- STN (subthalamic nucleus) or GPi (globus pallidus interna)
  the main targets for treating the cardinal motor symptoms of PD as well as reducing dyskinesias and "off time" in patients with motor fluctuations
- Vim nucleus of thalamus
  target for patients with severe PD tremor without other PD symptoms (this target is also beneficial for treating patients with "essential tremor")

Severe parkinsonian tremors may not improve dramatically on dopaminergic medications.

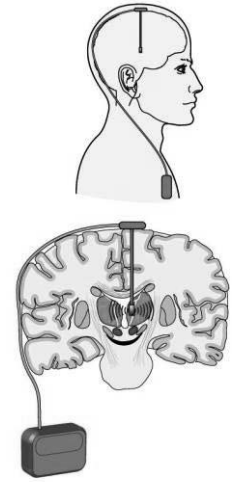
DBS can be of dramatic benefit for reducing severe tremors in Parkinson disease or essential tremor.

- This is the one situation where DBS will reduce a PD motor symptom that does not respond to levodopa.
- Other “non-dopaminergic” symptoms such as speech problems, severe freezing of gait, retropulsion, or axial symptoms do not improve with DBS.
- DBS will not eliminate “non-motor” problems in PD.

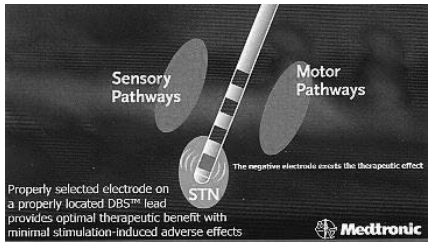
Who should perform “deep brain stimulation” ?

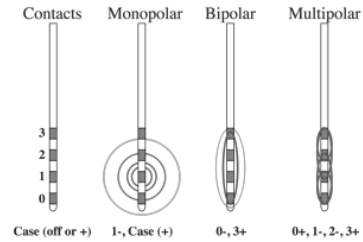
For best results referral should be made to an <u>experienced multidisciplinary team</u> (neurologist, neurosurgeon, psychiatry or neuropsychology, nursing) for

- pre-operative assessment to assure proper patient selection
- accurate surgical implantation of the electrodes
- expert programming of the pulse generator to maximize benefits and avoid side effects
- long-term follow-up and monitoring

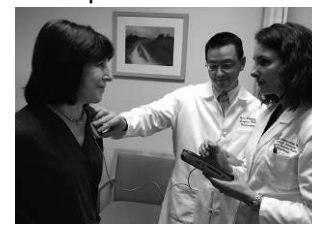


Programming the DBS pulse generator





The implanted electrodes have multiple contact points, each of which is stimulated to determine the setting that produces the optimal benefit for motor symptoms without causing side effects.

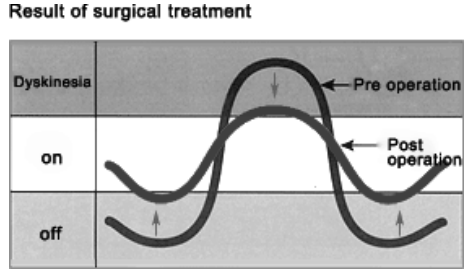


Parameters that are adjusted include:

- voltage
- pulse width
- frequency of stimulation
- field of stimulation

Multiple visits over a period of several months after surgery might be necessary to achieve optimal DBS programming.

What is the best outcome that can be expected from DBS in properly selected cases ?



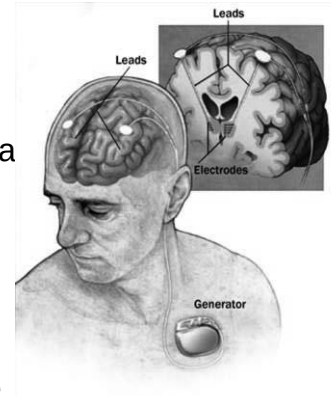
- Less “off” time and more “on” time
- Less tremor
- Less dyskinesia
- Some reduction in the amount of oral medication needed to treat Parkinson disease

Limitations of "deep brain stimulation"

- DBS is not a "cure" for PD.
- DBS does not halt the gradual progression of Parkinson disease.
- It is reasonable to expect results from DBS comparable to when the levodopa is "working":

  more "on" time but with

  less dyskinesia
- Medications can often be decreased but seldom eliminated.
- Optimal results from surgery may take months to achieve, and will be different for each patient.



Limitations of "**deep brain stimulation surgery**"

- DBS is very helpful for treating intractable tremors, dyskinesia, and motor fluctuations.

However:

DBS will <u>not</u> palliate other symptoms that do not respond to anti-parkinson medications:

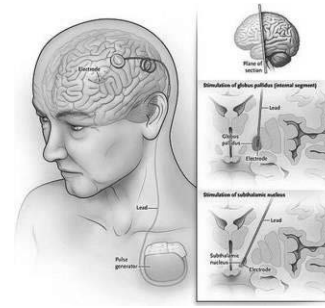
- Impaired speech (dysphonia, dysarthria)
- Dysphagia / swallowing problems
- "On" period shuffling or "freezing gait"
- Retropulsion / postural instability
- Anxiety, depression
- Cognitive / behavioral problems
- Dysautonomia
- Sleep disorders

do **<u>not</u>** benefit from DBS. If these are major symptoms, DBS should not be recommended.

Complications of “deep brain stimulation”

Surgical complications:

- Intracranial bleeding (0.5-3%): (often asymptomatic)
- Seizures (1%)
- Subtle cognitive deficits



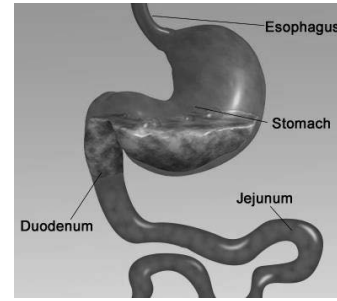
Device complications can occur 20% of cases over time:

- Infection
- Lead fracture
- Pulse generator malfunction
- Lead migration

Battery change is required every several years. Patients with “extended life batteries” require less frequent battery change, but need to recharge their battery nightly.

Continuous infusion of carbidopa/levodopa gel directly into the jejunum (“duopa”)

- Levodopa is absorbed into the bloodstream from the jejunum and <u>not</u> through the gastric mucosa.
- Infusion of carbidopa levodopa intestinal gel (“duopa”) directly into the jejunum avoids problems related to delayed gastric emptying that potentially contribute to erratic or delayed responses to oral levodopa therapy.
- More stable levodopa levels can reduce fluctuating symptoms in PD



“carbidopa/levodopa intestinal gel”

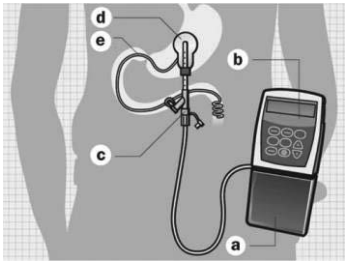
(marketed in the US as “duopa” and Europe as “duodopa”)

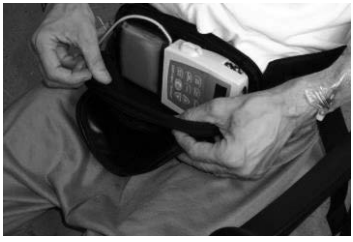
L-dopa 20mg/ml

plus

carbidopa 5mg/ml

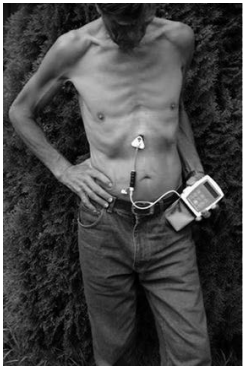
in a carboxycellulose gel that is infused **directly** and **continuously** via a J-PEG tube (gastrostomy tube with extension into the jejunum) using a programmable pump that precisely controls the rate of infusion.





Why a “programmable pump” ?

- The amount of carbidopa levodopa intestinal gel infused can be precisely **titrated** and **adjusted** to give the optimal amount of levodopa that the patient requires to control motor symptoms.
- “**booster doses**” of carbidopa levodopa intestinal gel can be self administered via the pump if needed to ameliorate transient “off” symptoms that might occur despite the continuous infusion.



Why continuous infusion ?

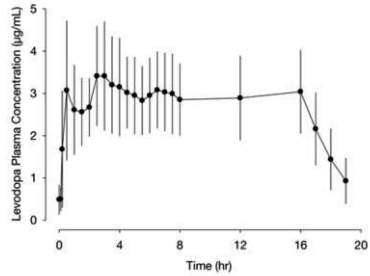


Figure 1. Plasma Concentrations (mean ± standard deviation) versus Time Profile of Levodopa with DUOPA (levodopa, 1580 ± 403 mg; carbidopa, 366 ± 92 mg) 16-Hour Infusion

Continuous infusion of medication directly into the jejunum significantly reduces the fluctuations in blood and brain levels of levodopa that contribute to the “on” and “off” symptoms in patients with PD.

Clinical trials of duopa vs oral therapy:

Randomized prospective trials compared:
Duopa infusion + placebo pills
versus
Placebo infusion + oral carbidopa/levodopa
Results:

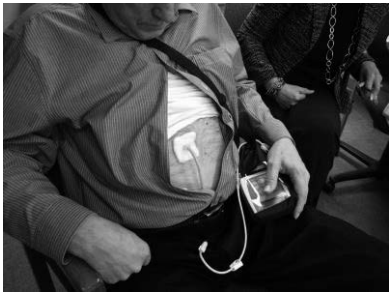
- Significantly more “on” time
- Fewer dyskinesias

in the patients receiving the carbidopa levodopa intestinal gel infusion (duopa) compared to standard treatment with regular oral carbidopa/levodopa.

These studies were performed prior to the availability of rytary (extended release carbidopa/levodopa) which has a longer half-life, and is therefore often more effective than regular carbidopa/levodopa in controlling fluctuations.

Who is a potential candidate for carbidopa/levodopa intestinal gel infusion?

1. Patients with PD who respond well to levodopa, but with fluctuations that cannot be well controlled despite adjusting oral medications
2. Patients with frequent “off” periods or dyskinesias
3. Patients require a very reliable care-partner to help operate and manage the care of the infusion pump and tubing.



Who is a potential candidate for carbidopa/levodopa intestinal gel infusion?

Duopa can be considered when oral therapies do not adequately control fluctuating symptoms:

- In patients who are reluctant to undergo deep brain stimulation surgery
- In elderly patients with mild cognitive decline who might not be ideal candidates for deep brain stimulation surgery

However:

- Not recommended in patients with severe dementia or dopaminergic psychosis
- Not recommended for patients do not respond well to carbidopa levodopa or whose most significant clinical symptoms are not due to lack of dopamine
  (such as speech or swallowing problems, severe postural instability, freezing of gait, behavioral problems)

DBS or DUOPA for fluctuating symptoms ?

There are no “head to head” comparative trials.

“pros” for DBS:

- Simplicity – no daily manipulation of device by the patient is necessary
- No need to wear a J-PEG tube or pump
- More likely to benefit severe tremors or dyskinesias

“pros” for duopa:

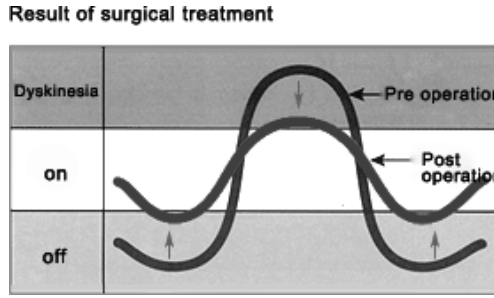
- No brain surgery
- No need for battery replacement surgery
- No need for oral carbidopa levodopa during the day
- Can be used in patients with mild dementia

In summary:

Levodopa does not “stop working”, but

- Neurodegeneration continues over time, resulting in gradually worsening symptoms, fluctuations in response to treatment, and the potential appearance of non-dopaminergic symptoms .
- Adjusting the timing and doses of oral medications successfully controls fluctuations in most cases.
- Once the optimal treatment regimen is found, it is very important for patients with fluctuating symptoms to comply with their medication schedule.
- Over-medication with dopaminergic therapies can cause serious side-effects: dyskinesias, hallucinations, psychosis, impulse control disorders, dopamine dysregulation syndrome
- Under-medication can lead to immobility, increased disability, and greater risk of falls.
- Important “non-motor” symptoms must be evaluated and treated.

In summary:



- DBS and duopa infusion may be beneficial for reducing motor fluctuations and dyskinesia for patients whose symptoms are not well controlled after adjusting oral medications.
- DBS is particularly helpful for the subgroup of patients with severe tremors that are not adequately palliated by medications.
- DBS and duopa are **not** beneficial for:

cognitive / behavioral problems, autonomic dysfunction, or "non-dopaminergic motor symptoms" such as retropulsion, freezing of gait, dysphagia, dysphonia, or dysarthria

Expectations must be realistic:

- Duopa and DBS
  are not "cures" for PD,
  do not alleviate every symptom, and
  are not indicated for everyone,
  but can be extremely helpful in
  properly selected cases
- If "non-motor problems" or "non-dopaminergic motor problems" (motor symptoms that are not helped by levodopa) are the major cause of disability, DBS or duopa are unlikely to be beneficial, and should not be recommended (the exception being severe tremors, which improve with DBS despite not necessarily responding dramatically to dopaminergic medication).

No Cure Does Not Mean No Hope!

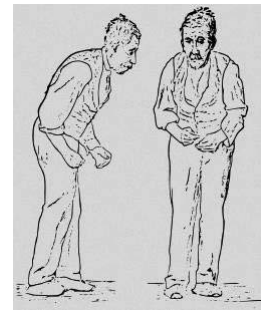
NON-DOPAMINERGIC MOTOR PROBLEMS

Unfortunately, as Parkinson disease progresses, patients often develop motor symptoms that are not caused by lack of dopamine and consequently do not reliably respond to dopaminergic therapies.

The loss of dopamine producing neurons does not explain all of the symptoms of PD: **Many of the motor symptoms in advanced PD are largely or partly "non-dopaminergic"**

- Postural instability / "retropulsion" "propulsion" (falling backward or forward)
- "freezing gait": inability to initiate or sustain gait
- Festinating gait
- Dysarthria- hypophonia
- Dysphagia
- Drooling
- Dystonia
- Camptocormia ("bent spine")

Unfortunately, these symptoms do not respond well to dopaminergic therapies.



Freezing of gait ("FOG")

- FOG is a failure of the "automatic" motor program of gait
- Feet intermittently feel "magnetized" or "glued" to a spot
  (the patient is transiently unable pick up their feet to produce effective stepping)

Common clinical manifestations:

- Inability to initiate gait or walk through doorways or turn to change direction ("start hesitation" or "turn hesitation")
- Inability to sustain gait while walking down a straight corridor

FOG is disabling and frustrating to the patient, and often leads to falls and significant disability.

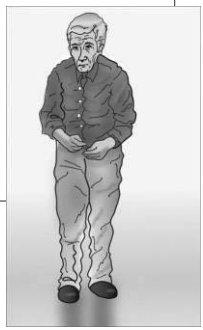
Freezing of gait is often an intermittent phenomenon that can be provoked by:

"emotional" triggers:

- Time constraints (rushing)
- Stress
- Anxiety
- Anger
- Fear of freezing

"environmental" triggers:

- Gait initiation
- Narrow passages
- Doorways
- Elevators
- Busy crowds
- Turning



Stress and the fear of "freezing gait" is a potent trigger for some patients.

"freezing of gait" ("FOG") in PD

In Parkinson disease:

- FOG can occur as an "off" phenomenon
  (which might respond to adjusting the carbidopa levodopa schedule)
- FOG can also occur in a background of good general mobility ("on" state FOG)
  (which responds poorly to adjusting the levodopa dose or other dopaminergic therapies, and will not improve with deep brain stimulation surgery)

Freezing of gait is not an early symptom in PD, and generally appears many years after diagnosis. Prominent freezing early in the course raises the possibility of a "parkinson plus" disorder, such as progressive supranuclear palsy.

Treating gait freezing in Parkinson disease

- Optimize levodopa therapy to reduce "off" period freezing

When "freezing" occurs:

- The patient must consciously come to a complete stop to reduce the risk of falling

After a brief pause (e.g. "count to 3"):

- The patient should lift one leg high and "march" to a cadence or tune

  or

- Step over a target (e.g. laser beam, or inverted cane, or a line on the floor)

These maneuvers can help patients whose feet have become "stuck" to re-initiate gait.

Treating gait freezing in Parkinson disease

- Physical therapy and gait training programs (such as the “big program” for Parkinson disease) have been developed to help reduce the impact of “freezing of gait”.
- Specialized walkers and laser devices might benefit some patients
- Patients can experiment with a wide variety of compensation strategies to find one that best helps reduce their gait impairments.
  For example:
  - marching
  - stepping over an inverted cane or laser beam
  - rhythmic cues (e.g. the beat of a metronome)
  - shifting weight in place prior to stepping
  - using walking aids or supports
  - crossing legs while walking
  - walking side-ways or backward
  - virtual reality goggles

Factors predisposing to falls in Parkinson disease

- Loss of balance with sudden changes in position (e.g. while turning or transferring)
- “freezing of gait” and festination
- “off” spells with immobility
- Postural instability - retropulsion or propulsion
- Multi-tasking, carrying packages, and distractions while walking
- Orthostatic hypotension
- Carelessness
- Impulsivity and poor judgment

are important factors predisposing patients to fall

a dangerous formula: impulsivity and poor judgement

impulsivity + poor judgement + imbalance = falls

cautious patients with good judgement are at much lower risk of falling.

Patients must move mindfully at all times!

Cognition and risk of falling

- "Poor self-awareness of limitations" and "impulsivity" result in an increased risk of falling
- "multi-tasking", carrying packages or purses, and distractions all increase the risk of falling

Patients with Parkinson disease must move MINDFULLY !
Avoid distractions!
Wait for help if needed.

- Do not carry packages, reach for items on high shelves, or stand on chairs or ladders!

Practical home safety tips to share with patients

- Use non-skid mats in the bathtub and shower
- Install secure safety bars in tub, shower, and near toilet
- Use shower chair and elevated toilet seat
- Remove throw rugs and other tripping hazards
- Install night lights in bathroom
- Position shelves so they are not too high or too low
- Place commonly used items within easy reach
- Place secure handrails on all stairways
- Make sure the handrails are as long as the stairway

Practical home safety tips to share with patients

- Do not stand on chairs or stepladders
- Arrange furniture to create clear pathways
- Do not use wax or polish that makes floors slippery
- Keep floors dry and clean up water on floor immediately
- Turn on lights to avoid falling in the dark (e.g. motion activated night lights)
- Wear supportive shoes that fit well
- Do not wear high heels or “flip flops”
- Keep a telephone by the bedside and wear an alarm device in order to promptly summon help if a fall occurs.

Home modifications that might be considered for some patients with advanced PD

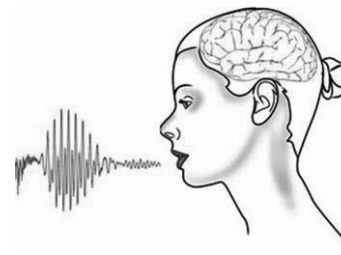
- Electric lift chair
- Electric “hospital bed”
- Stair glide
- Wheelchair or electric mobility device
- Ramps for wheelchair patients
- Railings or grab bars in shower, bathroom, and hallways
- Bedside commode chair
- Raised toilet seats

A formal “home safety evaluation” by an occupational therapist is valuable for determining the most appropriate and useful safety options for the patient.

Speech problems in Parkinson disease

Bradykinesia and rigidity of the speech musculature and poor control of respiration can lead to:

- Softening of voice (hypophonia)
- Monotonal speech
- Poor articulation



These problems are mild in early PD, but might gradually worsen, leading to severe restrictions on effective communication:

- Severe hypophonia and dysarthria
- Incomprehensible mumbling
- Words running into each other (tachyphemia)
- Oral festination

Adjusting dopaminergic therapies does not eliminate significant speech problems in PD, and speech therapy is appropriate.

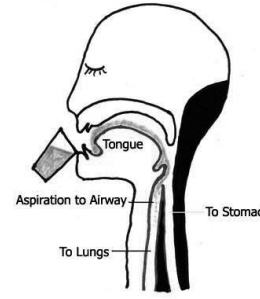
Speech therapy is helpful in Parkinson disease

- PD patients with soft speech (hypophonia) often paradoxically think their voice has normal volume.
- To improve hypokinetic dysarthria, patients are taught to slow their pace of speech and enunciate more deliberately.
- Patients with hypophonia patients are taught to place volume at the forefront of their consciousness ("think loud"): (e.g. the "Lee Silverman Voice Therapy program" which is part of the "big and loud" program for Parkinson disease)
- Patients must be motivated to practice their speech exercises on a daily basis.

Swallowing problems in Parkinson disease

Impaired oro-pharyngeal motility is a common and potentially very serious problem in PD, leading to dysphagia and risk of aspiration:

- Dysphagia can persist despite optimizing dopaminergic medications
- The initial symptom is often difficulty clearing saliva or coughing while drinking liquids or coughing after meals:
  ask patients whether they are experiencing these symptoms!
- Dysphagia puts patients at risk for poor nutrition, weight loss, aspiration, and pneumonia



Swallowing problems in Parkinson disease

- Formal speech therapy and swallow evaluations are appropriate if dysphagia is suspected.
- Video-fluoroscopy is often indicated to confirm and assess the severity of the problem.
- Dietary modifications and altered food consistency (such as use of “thickeners” or soft solids or pureed diets) can reduce the risk of aspiration.
- Video-assisted swallowing therapy, expiratory muscle strength training, and surgical interventions may benefit some patients.

Hints to reduce the risk of aspiration in PD

- Do not eat too fast! don’t try to keep up with others!
- Slower eating with smaller bites!
- Thicker consistencies and thickened liquids can decrease the tendency to aspirate
- Diet consisting of soft or pureed foods if necessary
- Sit upright at all times when eating or drinking
- “chin-tucking” to facilitate swallowing
- Intermittent small sips of fluids to “wash down” solids
- Cooled liquids are easier to swallow than warm liquids

Weight loss in Parkinson disease

Gradual weight loss is common in PD:
weigh your patients regularly

Causes of reduced caloric intake:

- dysphagia, anorexia (possibly medication induced), depression, G-I dysfunction

Causes of increased energy expenditure:

- tremor, dyskinesia, rigidity.

Weight loss tends to be most notable in persons with more severe motor symptoms, and in those with cognitive decline.

Concomitant medical causes of weight loss must always be considered.

Evaluation by a dietician or nutritionist is often appropriate.

Sialorrhea (drooling) in Parkinson disease

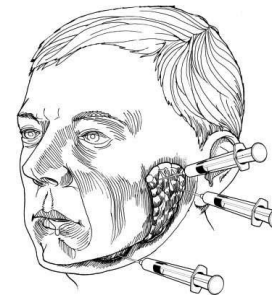
- Spontaneous swallowing frequency may be reduced in Parkinson disease
  (similar to reduction of other subconscious automatic behaviors, such as decreased blinking or diminished arm swing while walking).
- Drooling is caused by reduced swallowing rather than increased saliva production.
- The saliva that is not swallowed tends to run out of the mouth.
- Drooling often occurs during sleep, and patients may need to place towels over their pillow or bed sheets.
- Drooling is a potential source of great embarrassment to the patient.

Treatment of sialorrhea in PD:

- Optimize dopaminergic therapy to reduce akinesia and “off” time.
- Chewing gum or sucking on a sugar-free mint is helpful for most patients with mild drooling.
- 1% atropine solution: 2 or 3 drops given orally under tongue
- Anticholinergics (glycopyrrolate)

(caution: beware of anticholinergic side effects: confusion, psychosis, urinary retention, constipation)

- Botulinum toxin injections into the salivary glands reduces saliva production, and can reduce drooling in severe cases.



Unusual postural abnormalities in PD

- Cervical dystonia
- “dropped head”
- Camptocormia
  (“bent spine”)
- Pisa Syndrome
  (lateral flexion)

These symptoms usually do not respond to dopaminergic therapies.

“Dropped head”, Pisa syndrome, and camptocormia are more commonly seen in **multiple system atrophy** than in Parkinson disease.

Botulinum toxin injections can help alleviate painful cervical dystonia.

Management of motor symptoms that do not respond to medical treatment

A multi-disciplinary approach is needed to help manage advanced symptoms of PD:

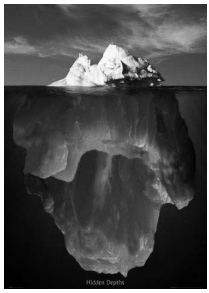
- Physical therapy
- Occupational therapy (including a home safety evaluation)
- Speech therapy
- Supervised exercise programs
- Psychological support for patient and care-partner should be part of the treatment program !

NON-MOTOR PROBLEMS in PARKINSON DISEASE

Parkinson disease is more than just a “movement disorder”. There is a very high prevalence of behavioral and psychiatric disorders, autonomic dysfunction, and sleep disorders that accompany or may even precede the motor symptoms.

“holistic” approach to PD:

Parkinson disease is diagnosed on the basis of **“motor”** symptoms, but these are often just the “tip of the iceberg”:



“non-motor” features are often the major source of disability and cannot be neglected!

Redefining Parkinson disease

Parkinson disease is a neurodegenerative disorder with multiple potential causes and predisposing factors that is diagnosed on the basis of typical motor signs and symptoms. However, the disease also manifests a spectrum of

- Behavioral / psychiatric issues
- Cognitive problems
- Autonomic dysfunction
- Sleep disorders

Assessing the response to treatment: "quality of life" in Parkinson disease

In most cases feeling "better" is not enough:

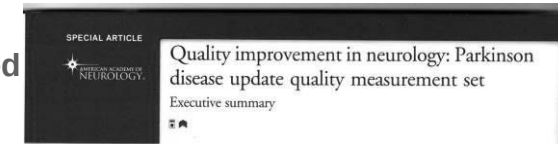
Physicians often forget

PATIENTS WANT TO FEEL **"GOOD"** NOT JUST "BETTER".

The non-motor symptoms are often a major source of distress or disability.

Evaluating **non-motor** as well as **motor** problems is important at every visit.

Issues to be addressed at each office visit:


SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

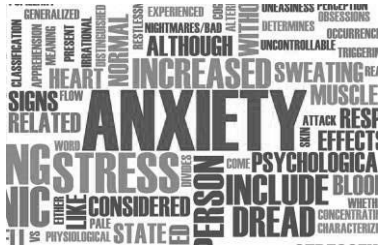
Quality improvement in neurology: Parkinson disease update quality measurement set

Executive summary

- Annual review of Parkinson disease diagnosis
  (signs suggesting an alternative diagnosis may appear as time goes by)
- Careful review of medication schedule
- Querying about medication-related complications
- Assessment of psychiatric symptoms
- Assessment of cognitive dysfunction or impairment
- Evaluating for autonomic dysfunction
- Assessment speech, swallowing, nutrition
- Querying about sleep – wakefulness disturbances
- Querying about falls and mobility issues
- Reviewing PD rehabilitation and exercise options
- Assess care-giver burden and need for assistance

Neurology 2016; 86: 2278-2283

There is an increased prevalence of **anxiety** and **depression** in Parkinson disease



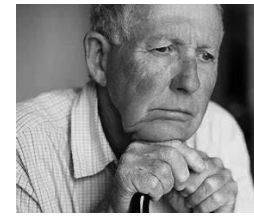
Mood and anxiety disorders may precede the onset of motor symptoms in some patients with PD.

New onset of depression in mid-life is often a harbinger of subsequent neurodegenerative disorders such as

- Parkinson disease,
- Dementia with Lewy bodies, or
- Alzheimer's disease.

Depression in Parkinson Disease

- Very common!
  Mood disorders and depression affect between 20-50% of persons with PD
- Depression is often an *intrinsic phenomenon* that is part of the disease and might even precede the diagnosis of PD.
  ("endogenous depression")
  new onset of depression in mid- to late- life is often a precursor of neuro-degenerative diseases such as PD, dementia with Lewy bodies, Alzheimer's disease



- Depression may be triggered as a reaction to the illness ("reactive depression")
  (for example, after loss of employment or inability to participate in cherished activities).

Both phenomena may co-exist

There is a spectrum of mood and depressive disorders in Parkinson disease:

- Adjustment disorder
- Dysthymia – dysphoria
- Minor depression
- Mood fluctuations as part of the "non-motor fluctuations" of PD
- Demoralization
- Anhedonia
- Major depression

Distinguishing these disorders is important in guiding management.

Every patient who is unhappy is not necessarily depressed.

Emotional features of major depression

- Persistent sadness
- Lack of interests
- Lack of enjoyment
- Overwhelmed / anxious
- Irritability
- Pessimism
- Hopelessness
- Negative ruminations
- Negative view of self
- Guilt
- Morbid thoughts
- Suicidal ideation
- Inability to cope

Depression is often under-diagnosed in PD, but can also be over-diagnosed:

Some common signs seen in Parkinson disease may mimic symptoms of depression:

- "sad" "masked" facial expression
- Slowness of thought and movement
- Difficulty concentrating
- Sleep disturbances
- Apathy
- Lack of energy
- Pseudo-bulbar affect / crying

Core symptoms of depression are:

- Low mood / sadness
- Negative thinking

"pseudo-bulbar affect"

"Pseudo-bulbar affect" refers to a markedly reduced threshold for crying (or laughing) in response to minimal emotional stimuli.

- Patients often report an incongruity between the emotional display and what they are truly feeling.
- The symptoms can be quite embarrassing.

The crying spells give the impression that the patient is sad or depressed when this is not necessarily the case.

Pseudo-bulbar affect sometimes occurs in PD, but is more likely noted in other parkinsonian disorders such as progressive supranuclear palsy or vascular parkinsonism.

Anhedonia and demoralization in Parkinson disease

Anhedonia: an inability to experience pleasure from activities previously found to be enjoyable

Demoralization: feelings of failure, hopelessness, helplessness, and incompetence

These emotional states are often associated with major depression, but are not a *sine qua non* of depression. Anhedonia and demoralization also occurs in some persons with Parkinson disease who are **not** depressed.

Parkinson disease and anxiety

- Anxiety is highly prevalent in Parkinson disease, affecting 20-40% of patients.
- Anxiety and depression often co-exist.
- The degree of anxiety does not necessarily correlate with the severity of physical or cognitive impairment.

However

- The level of anxiety can fluctuate dramatically in patients experiencing motor and non-motor fluctuations.

Anxiety not only impairs mental health, but will greatly exacerbate tremor, dyskinesia, motor fluctuations, gait disorder, and other Parkinson disease motor symptoms.

Anxiety and Parkinson disease

- Many PD patients find that they become anxious, worried, nervous, or easily upset by situations that would not have bothered them in the past.
- Some become anxious for no apparent reason.
  ("free floating anxiety")

"vicious cycles":

Anxiety often exacerbates tremor, dyskinesia, freezing of gait, and other motor symptoms, which in turn creates more anxiety.

"Off spells" can cause anxiety, and anxiety can trigger "off spells".

Anxiety can be misdiagnosed

Some symptoms of Parkinson disease can *overlap* with symptoms of anxiety, giving the impression that the patient is anxious when this is not the case :

- Akathisia
- Restlessness
- Difficulty concentrating
- Sleep disturbances
- Tremor
- Dyskinesia

Core symptoms of anxiety are:

- Excessive worrying
- Excessive fears

"***stress***" and **anxiety adversely affect motor function in Parkinson disease**

Stress and anxiety exacerbate involuntary movements:

- Increased tremors
- Increased dyskinesias

and can potentially trigger:

- Gait problems
- "freezing of gait"
- Immobility
- Motor fluctuations
- "off" spells

Anxiety also magnifies and dramatizes the patient's perceptions of the severity and negative impact of their motor symptoms.

"non-motor fluctuations": anxiety and mood can fluctuate dramatically in addition to fluctuations in motor function:

While "OFF"

- Severe despondency
- Self deprecating
- Anxiety
- Panic
- Inner shakiness (akathisia)
- Hopeless feelings

While "ON"

- Euthymia
- Energetic
- Hypomania

"*social avoidance*" is common in parkinsonism

- Social situations can trigger increased anxiety.
- Anxiety can exacerbate parkinsonian symptoms (such as tremor, dyskinesia, "off" spells, freezing gait) and create unpleasant self-consciousness.

Consequently:

- The patient prefers to stay home to avoid the stress and potential embarrassment.

Social avoidance leads to increased disability in PD !

Don't let Parkinson disease put your patients under "***house arrest***"

Some patients become reluctant to leave the house:

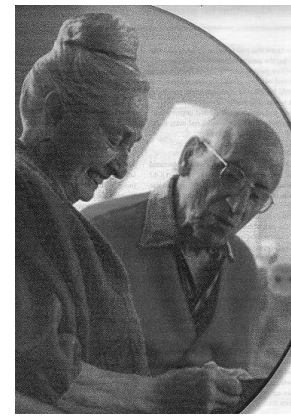
"I'm too embarrassed"
"People are looking at me"
"I don't want to make a fool of myself"
"I don't want to bother anyone"
"I'm afraid of falling"
"It's too much effort"
"It takes too long to get ready"

Social isolation leads to decreased quality of life, depression, and worse long-term outcomes. Encourage patients to participate in activities out of the house as often as possible (exercise classes, support groups, lectures, social organizations, church groups, etc.): enlist family members to arrange transportation and assist the patient if necessary.

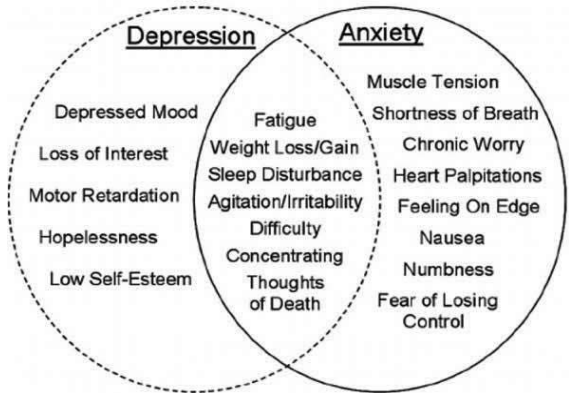
Anxiety and depression in PD

Depression and anxiety often coexist:
in one study
90% with anxiety had mood disorders
67% with depression had anxiety:

- Generalized anxiety disorder
- Panic disorder (often triggered by "off spells")
- Phobic disorder (social phobia and agoraphobia)
- Anxiety "not otherwise specified" (anxiety disorders not meeting criteria for specific DSM sub-types, such as episodic anxiety triggered by "off spells")



Treating anxiety and depression in PD:



- Anxiety and depression must be assessed, as the disorders are disabling but potentially treatable!
  The patient's "quality of life" often depends more on management of anxiety and depression than on the severity of parkinsonian motor symptoms.

When to seek help for anxiety and depression

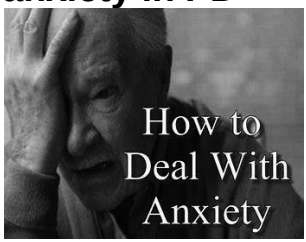
- Inability to function
- Loss of energy or interest
- Feeling out of control
- Panic attacks
- Increased consumption of alcohol or medications
- Difficulties in sleeping or waking
- Inability to concentrate or memory problems
- Increased irritability
- Thoughts of suicide

Depression and **anxiety** in PD are **treatable**:

- Optimize PD medications to reduce “off” time
- Counselling
- Psychotherapy
- Exercise
- Socialization
- Support groups
- Education seminars
- Medications
- Electro-convulsive therapy is an option for PD patients with severe refractory depression that is not responding to medications

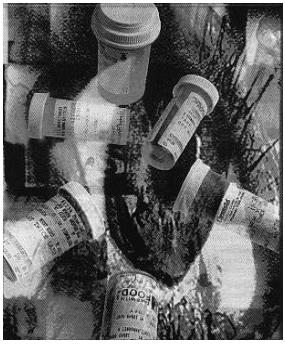
The physical, social, and emotional benefits of regular participation in exercise classes should not be over-looked.

Management of anxiety in PD



- Regular participation in exercise programs can reduce stress and anxiety
- Psychotherapy, counselling, and relaxation techniques
- Cognitive behavioral therapy
- Adjust PD medications to reduce “off” time and dyskinesias
- Antidepressants (especially if there is concomitant depression)
- Benzodiazepines? use with caution! potentially dangerous:
  addiction potential,
  impaired balance / increased fall risk,
  excessive sedation

Some of the many medications that might be considered to treat major depression in PD:



Anti-depressant for patients who also experience insomnia and weight loss:

- Mirtazapine

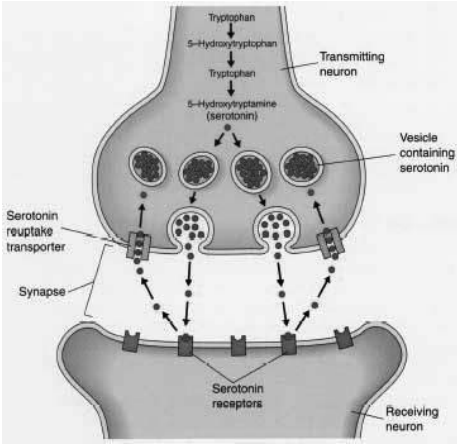
Anti-depressants for patients who also experience severe anxiety

- “SSRIs”: escitalopram, paroxetine, sertraline, fluoxetine

Anti-depressants that might also reduce apathy and fatigue:

- Venlafaxine
- Bupropion

Treating depression with medications:
explaining the mechanism of action to the patient might improve compliance



- Antidepressant medications alter the levels of *serotonin*, and/or *norepinephrine*, and/or *dopamine* in the brain (neurotransmitters that are important in mood regulation)
- Antidepressants are typically started in low dose, and slowly increased until they reach levels known to be "therapeutic"
- Once a therapeutic dose is reached, it might take 4-6 weeks before improvement in mood is noted

Treating depression with medications:
counsel patients to improve compliance

- Unfortunately, the lack of prompt benefit often causes patients (and the doctors treating them) to lose faith and prematurely abandon treatment.
- It is important to explain this to the patient so they will commit to a full course of treatment (~6 weeks) in order to give the medication time to work before changing course.

Important non-medicinal approaches helpful in treating depression in PD:

- Individual and group therapy
- “cognitive behavioral therapy”
- Participation in PD support groups
- Attend PD educational seminars
- Regular exercise programs
- Staying socially active

are all associated with better outcomes than just treating depression with medication alone.

A common clinical scenario:

Spouse *complains :*

What is wrong with my husband?

“he doesn’t make plans or start activities”

“he procrastinates”

“he has nothing to say” “very quiet”

“no motivation”

“not concerned”

“he used to be the life of the party”

“lacks interests or enthusiasm”

“he has become a couch potato”

“never gets anything done”

The patient *says:*

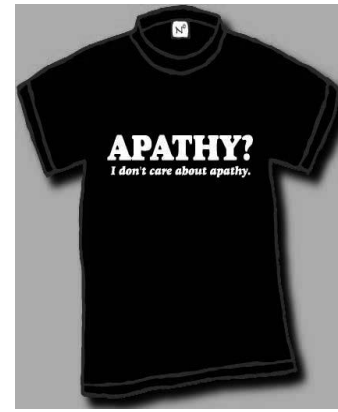
“I’m all right”

Clinical manifestations of apathy:

Apathy is a common and disabling feature of Parkinson disease, and can occur at any stage of the disease.

Clinical manifestations include:

- Lack of motivation
- Lack of concern / indifference
- Reduced interest
- Reduced participation
- Problems initiating activities
- Problems completing activities
- Slowed thought processes
- Lack of ideas or conversation
- Loss of curiosity
- Lack of pleasure
- Flat affect



Apathy and depression in Parkinson's disease

Apathy can accompany depression, or occur as a specific neuropsychiatric syndrome in persons who are not depressed.

One study of 50 patients with Parkinson disease found:

- 12 % had APATHY without depression
- 20% had DEPRESSION without apathy
- 30% had both APATHY and DEPRESSION

Is it depression or apathy or both ?

The major criterion for diagnosis of depression in a patient with profound apathy is the patient's mood:

- Depressed patient:
  inner sadness / negativity
- Apathetic patient:
  emotional dullness

The distinction is important because apathetic patients are potentially misdiagnosed with depression, and inappropriately treated with medications that might exacerbate apathy.

"Portrait of Patience Escallier" by Vincent van Gough

"apathy" is common in disorders affecting limbic-frontal-subcortical circuits

- Parkinson disease
- Traumatic brain injury
- Post-anoxic brain injury
- Alzheimer's disease
- Multi-infarct states
- HIV dementia
- "Parkinson-plus" disorders
  (e.g. progressive supranuclear palsy)
- Normal pressure hydrocephalus
  (symptomatic adult hydrocephalus)

Apathy is a manifestation of brain dysfunction in these conditions, and not a psychological response to physical impairment (as the family or treating physician might erroneously suspect).

Why care about apathy ?

The patient is seldom concerned or distressed by their apathy, however

- Apathy greatly increases care-giver burden and distress.
- Apathy is often **misinterpreted** or **misdiagnosed** by the family**:**
  it is not willful or due to "laziness"
- Apathy reduces participation in daily activities, and is associated with worse long-term outcomes.

It is very frustrating for the family to see a previously dynamic and active person sit around and do nothing all day.
Explaining the diagnosis of apathy to care-partners and family enables them to better understand and cope with the patient's altered behaviors.

"**fatigue**" is common in Parkinson disease

"Fatigue" is a subjective sense of

- Tiredness
- Exhaustion
- Low energy

without necessarily feeling sleepy

Often characterized by

- Difficulty initiating or sustaining activities ("*physical fatigue*")
- Difficulty sustaining mental effort ("*mental fatigue*")

For some patients fatigue is one of the most disabling aspects of PD.

Fatigue in Parkinson disease

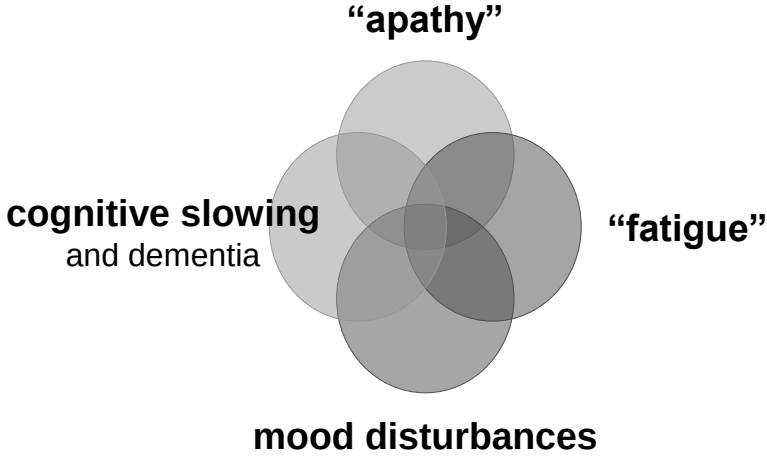
Fatigue is a common and independent nonmotor symptom in PD, but there are concomitant factors that can potentially contribute to this symptom:

- Insomnia or sleep disruption
- Orthostatic hypotension
- Medication side effects
  (e.g. PD meds, anti-anxiety drugs)
- Depression
- Deconditioning
- Concurrent medical problems
  (e.g. thyroid disease, anemia, etc)

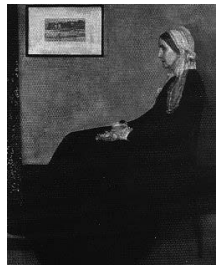
Parkinson disease patients commonly “run out of steam” in mid-afternoon. A brief nap may restore energy for these patients.

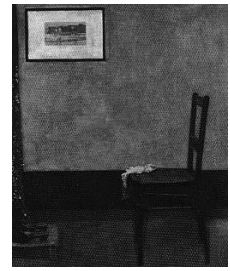
“overlapping syndromes”

apathy and fatigue can occur as independent entities or as concurrent features of mood or cognitive disturbances



Treatment of apathy and fatigue:





- Optimize anti-Parkinson medications to reduce “off” time
- Exclude concomitant medical conditions or medications that might contribute to symptoms
- Treat depression if it is a concurrent problem
- Counselling family members (who often misinterpret or misunderstand the patient’s symptoms)
- There is no medication that reliably alleviates apathy or fatigue, but occasional patients might benefit from stimulants or rivastigmine.

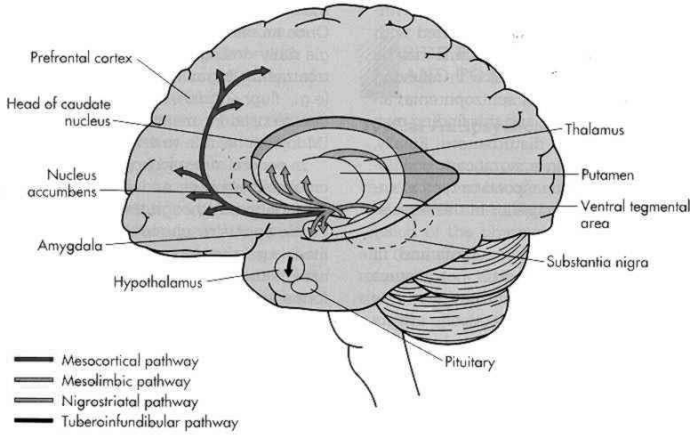
Iatrogenic problems in Parkinson disease: Medications are “double edged swords”

Behavioral and psychiatric problems can be caused or aggravated by the medications used to treat PD.

Avoid over-medication!
Avoid polypharmacy when possible!

Unfortunately, some behavioral side effects are idiosyncratic, and not due to “over-medication” or inappropriate use. Constant vigilance and careful monitoring of patients is appropriate in all cases.

Brain dopamine pathways



Dopamine is not only important in regulating motor function (the nigro-striatal pathway), but is also a neurotransmitter in meso-limbic and meso-cortical pathways that affect behavior, pleasure, and assessment of risk / reward.

What happens when you upregulate the dopaminergic system in Parkinson disease?

The “good”:

- The cardinal motor features of Parkinson disease improve

The “bad”:

- Dyskinesias
- Fluctuating symptoms
- Mild hallucinosis

The “ugly”:

- Impulse control disorders
- Severe hallucinations
- Delusions / full blown psychosis
- Dopamine dysregulation syndrome

CAUTION: risk of over-medication with potential dose related and idiosyncratic side effects !

Physicians must monitor patient's treatment regimens and behavioral symptoms closely to avert problems that might potentially be caused or exacerbated by medication !

- Intolerable dyskinesias
- Hallucinations
- Psychosis
- Punding
- Impulse control disorders
- "Dopamine addiction" (dopamine dysregulation syndrome)

Psychosis phenomenology: definitions

- Hallucinations- false sensory perceptions in the absence of external stimuli (hallucinations in Parkinson disease are usually visual)
- Illusions- misperception of actual stimuli
- Passage hallucinations –a sense that a vague object or shadow is passing through the peripheral field of vision
- Sense of presence – a feeling that someone is standing nearby
- Delusions – idiosyncratic false beliefs

Hallucinations in Parkinson disease:

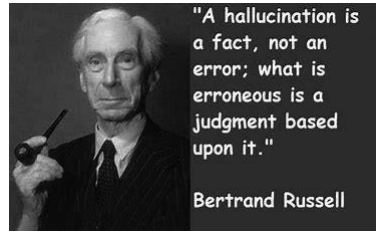
Ask about it ! Patients often will not mention illusions or hallucinations unless specifically queried.

- Mild visual hallucinations are a very <u>common</u> phenomenon, and may be as subtle as a brief shadow seen from the corner of the eye (the latter is called a “passage hallucination”).
- Mild stereotyped visual hallucinations are also common: (e.g. “little people”, bugs, or animals)
- Hallucinations in PD are often non-threatening, occurring with a clear sensorium.
- Hallucinations are often caused or exacerbated by the medications used to treat PD

However

- Hallucinations may seem quite real and terrifying: a first warning of incipient frank psychosis.

Typical hallucinations and illusions in PD:



- “Little children are in my bed”
- “there are bugs on the wall”
- “the fire hydrant looks like a little person”
- “I frequently see strange people outside my window”
- “A burglar is trying to enter my house”

In most cases the patient recognizes that the hallucinations or illusions are unreal, and is able to ignore them without acting or making false judgments.

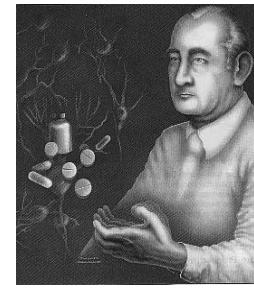
Psychotic patients cannot be easily convinced that they are hallucinating, and will act in response to the hallucinations.

Etiology of hallucinations in PD

- PD medications (dopamine agonists, carbidopa levodopa, anticholinergics, amantadine) can all induce or exacerbate hallucinations in the presence or absence of dementia.
- Patients with cognitive decline are more likely to experience hallucinations.

  Avoid over-medication!

  Eliminate the offending medication if possible



However

- Patients with PD dementia or "dementia with Lewy bodies" may experience hallucinations in the absence of medications and are very susceptible to medication induced psychosis.
- In the pre-levodopa era, advanced PD patients also experienced hallucinations in the absence of dementia.

Delusions in Parkinson disease:

- Delusions occur in 5-25% of PD patients who experience hallucinations, and seldom occur in the absence of hallucinations.
- Delusions are more likely in patients with impaired cognitive function (but are not always indicative of dementia).

The most common delusions in PD are "negative" / unpleasant:

accusations of spousal infidelity

"there are plots against me"

"people are stealing from me"

"Positive" delusions are uncommon:

"I won the lottery"

What causes psychosis in Parkinson disease ?

“Intrinsic factors” related to the disease

- Cognitive decline
- Dementia (PD dementia or dementia with Lewy bodies)
- Sleep deprivation
- Visual processing abnormalities
- Neurochemical changes in the brain

“Extrinsic factors”

- Dopaminergic therapies :
  dopamine agonists, levodopa
- Non-dopaminergic therapies:
  amantadine, anticholinergics
- Other medical conditions or medications that can trigger altered mental status

Who is at greatest risk for psychosis: (hallucinations, delusions, delirium) ?

- Older patients or patients with PD for many years
- Patients with cognitive decline or dementia
- Patients on higher doses of medication
- Patients on multiple medications
- Patients with REM sleep behavioral disorder
- Patients with sleep deprivation
- Patients with multiple medical problems

Institutionalization of patients with PD

- Cognitive changes / dementia
- Behavior changes
- Psychosis

are the most common problems leading to institutionalization of patients with PD, not motor impairment!

Care-partners are likely to comment:

"I can handle his lack of mobility, but I cannot handle his behavior".

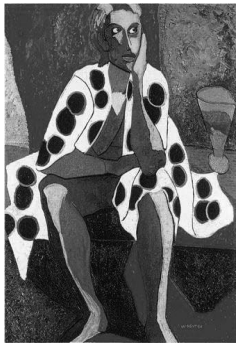
Preventing or effectively treating psychosis and behavioral problems are therefore crucial.

Treating psychosis in Parkinson disease

1. Review medications: taper or eliminate drugs that can cause hallucinations (avoid "polypharmacy")
2. Exclude other active medical issues (infection, metabolic problems)
3. Treat sleep disorders
4. Consider adding a cholinesterase inhibitor to enhance cognition (e.g. rivastigmine)
5. If hallucinations and delusions remain uncontrolled and problematic, adding an antipsychotic medication may become necessary.

Treatment of psychosis in PD:

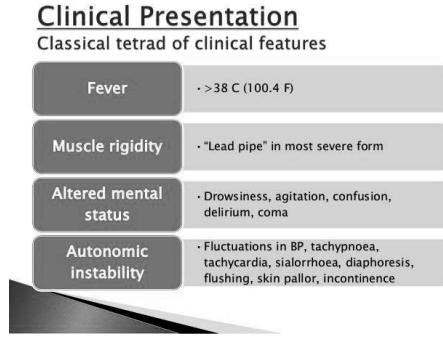
- Avoid polypharmacy: eliminate medications! :
  Anticholinergics
  Amantadine
  MAO-b and COMT inhibitors
  Dopamine agonists
  should be reduced or eliminated if possible
- Reduce or re-titrate levodopa!
  adjust carbidopa / levodopa schedule
- Add an antipsychotic if necessary:
  clozapine, quetiapine, and pimavanserin are the antipsychotic medications that have not been associated with worsening of motor symptoms of PD



Principles of re-titrating levodopa in patients with severe hallucinations or delusions

- Motor symptoms can often be managed with carbidopa/levodopa monotherapy, avoiding dopamine agonists and polypharmacy
- If reducing levodopa dose, do so gradually (e.g. by ~25%) and cautiously:
  (a sudden “drug holiday”, abruptly discontinuing levodopa, is dangerous and could trigger the “Parkinson hyperpyrexia syndrome”)
- Smaller levodopa doses given more frequently are less likely to cause psychosis than higher doses given less frequently
- Administer lower doses of levodopa later in the day in “sundowners”

“parkinson hyper-pyrexia syndrome”



- Clinically indistinguishable from “neuroleptic malignant syndrome”
- Triggered by abrupt withdrawal or marked reduction in dopaminergic medications in a patient with Parkinson disease
- Treatment involves supportive measures and promptly reinstituting dopaminergic treatment
- Serious! can result in permanent worsening of PD or death

Do not abruptly discontinue all dopaminergic medications!
If decreasing levodopa doses is necessary, do so gradually by no more than 25% -33% at a time.

Treatment of the neuropsychiatric complications of Parkinson disease

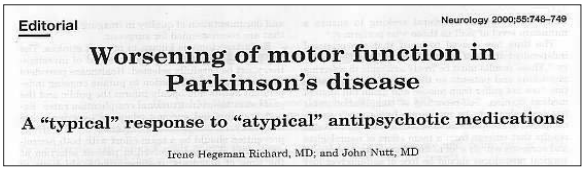
What do you do if eliminating dopamine agonist drugs and reducing the levodopa dose has resulted in worsening of parkinsonian motor symptoms?

“Doctor, my husband is no longer hallucinating or delusional, but now he is very stiff and immobile!”

Add an antipsychotic that is not associated with worsening of motor function in PD:

quetiapine, clozapine, or pimavanserin

If effective, these drugs might enable the patient to tolerate therapeutic levodopa doses with fewer hallucinations or delusions.



Editorial

Neurology 2000;55:748–749

Worsening of motor function in Parkinson's disease

A "typical" response to "atypical" antipsychotic medications

Irene Hegeman Richard, MD; and John Nutt, MD

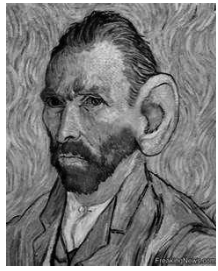
If an anti-psychotic medicine is absolutely necessary to control psychosis in PD, which drug should be used?

- 1st generation (e.g. haloperidol) and 2nd generation (risperidone, olanzapine, ziprasidone, aripipipazole, et al) antipsychotics all have a propensity to worsen parkinsonian motor symptoms, even in low doses.
- Avoid these medications in patients with Parkinson disease, dementia with Lewy bodies, and in elderly psychotic patients with tremors or mild "extrapyramidal" signs.
- **Quetiapine** and **clozapine** are the only traditional antipsychotics unlikely to exacerbate PD motor symptoms.
- **Pimavanserin** is a novel medication recently approved by the FDA for treating psychosis in Parkinson disease.

Medications for treating psychosis in patients with Parkinson disease

- Clozapine has been demonstrated to be beneficial in treating PD psychosis, and does not cause increased motor impairment

but has potential hematologic toxicity, and requires weekly neutrophil count monitoring.



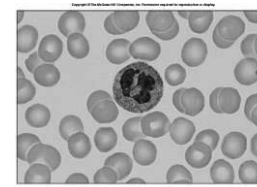
- Quetiapine has not shown similar efficacy to clozapine in treating psychosis in Parkinson disease, but is often used initially, as it does not have hematologic toxicity.

Start with low doses of quetiapine or clozapine and slowly titrate upward as necessary and as tolerated.

- Pimavanserin

Clozapine in Parkinson psychosis:

- Low doses (6.25 – 37.5mg/day) are often sufficient to treat psychosis in PD
  (much lower than the amount needed to treat schizophrenia)
- Control of psychosis may enable PD patients to safely tolerate higher doses of levodopa in order to improve motor function.



Side-effects:

- Sedation
- Orthostatic hypotension
- Agranulocytosis! might occur in 1% of treated patients and is not dose related (Neutrophil count monitoring is required weekly for the first 6 months then biweekly thereafter. Unfortunately the need for blood monitoring makes some physicians and patients reluctant to try this very valuable treatment option.)

Pimavanserin for psychosis in PD

Table 1 – Selectivity of Acadia's Nuplazid

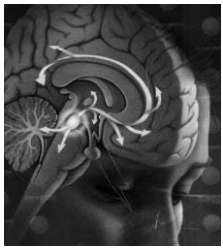
	5-HT_{2A}	D_2	H_1	Alpha
Nuplazid	Yes	No	No	No
Seroquel	Yes	Yes	Yes	Yes
Zyprexa	Yes	Yes	Yes	Yes
Risperidone	Yes	Yes	No	Yes
Clozapine	Yes	Yes	Yes	Yes

- Novel mechanism of action: selective serotonin 2A antagonist (not a dopamine blocking drug)
- One dose: 34mg daily
- Unlike quetiapine or clozapine, pimavanserin is not sedating
- Relative efficacy in controlling Parkinson disease psychosis compared to clozapine or quetiapine is uncertain
- FDA approved for PD psychosis (but is a very costly medication)

Impulsive and compulsive behaviors in Parkinson disease:

Replenishing brain dopamine can promote "*reward-seeking behavior*", triggering **irresistible** and **uncontrollable impulses** for:

- Gambling
- Shopping / spending
- Hypersexuality



This is particularly prevalent in patients receiving **dopamine agonists**:

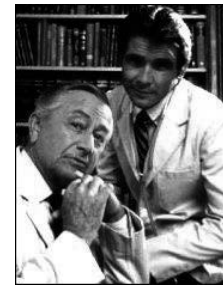
pramipexole, ropinirole, rotigotine

This risk is not unique to PD:
"impulse control disorders" also occur in patients who do not have PD but are receiving dopamine agonists for treating restless legs syndrome!

There are a variety of impulsive - compulsive behaviors that can occur in Parkinson disease

- Pathological gambling
- Hypersexuality
- Compulsive shopping
- Binge eating
- Reckless generosity
- Compulsive use of dopaminergic medications
- Dopamine dysregulation syndrome
- Computerism
- Hoarding
- Punding

Impulse control disorders (ICDs) in PD:



- This is an iatrogenic problem: ICDs usually occur in the context of treatment with a dopamine agonist:

  pramipexole, ropinirole, rotigotine

  (as monotherapy and especially when used in combination with carbidopa levodopa)
- Dopamine agonist use is associated with an increased risk of ICDs (as well as increased risk of hallucinations, psychosis, and other psychiatric complications)
- Approximately 15% of patients treated with a dopamine agonist will develop an impulse control disorder !

Impulse control disorders often elude detection

Why due clinicians often fail to detect ICDs?

- Many clinicians lack awareness of ICDs.
- Failure to warn and inform patients and family about possible behavioral side effects
- Failure to adequately screen patients for abnormal behaviors
- Even when asked, patients with ICDs will often deny or minimize problems (sometimes engaging in active deception).
- Family and friends need to be queried about unusual behaviors or urges that the patient might be experiencing.

Impulse control disorders (ICDs) **have potentially serious consequences**

For example

- Financial ruin caused by uncontrolled gambling
- Marital break-up due to sexual indiscretions
- Large malpractice verdicts against physicians who failed to warn patients receiving dopamine agonists about the risk of ICDs, or who failed to regularly screen patients on dopamine agonists for ICDs

Treating "impulse control disorders" (ICDs) in PD

- Taper and discontinue the dopamine agonist (managing motor symptoms with carbidopa/levodopa monotherapy) is often effective in eliminating the ICD
- Unfortunately, some ICD patients experience a "dopamine agonist withdrawal syndrome", producing symptoms similar to those seen in cocaine withdrawal, thus making it difficult to completely eliminate these medications.
- Psychiatric consultation and participation in psychotherapy and support programs (e.g. "gamblers anonymous")

“punding” in Parkinson disease

“Punding” refers to a compulsive fascination with purposeless tasks that are performed repetitively over and over again:

sorting & re-sorting / handling & re-handling the same objects
assembling and disassembling an object
reading & re-reading
excessive hobbyism or computerism or “walk-abouts”

The patient

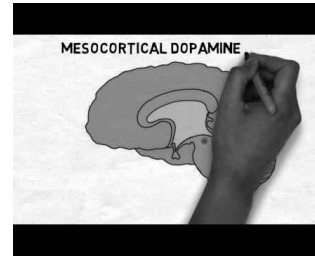
- Shows intense fascination or interest with the task
- Spends a great amount of time performing the activity
- Becomes irritable if interrupted or distracted
- Often develops sleep deprivation due to task

Punding behaviors can be triggered by dopaminergic therapies.

Dopamine dysregulation syndrome (DDS): “compulsive medication use”

(the overuse / abuse of dopaminergic medications)

The patient requests higher and higher doses of carbidopa/levodopa or other dopaminergic medications accompanied by:



- Complaints of progressive medication ineffectiveness
- Demands for frequent “rescue doses”
- “dopamine highs”
- Craving of dopaminergic medications
- Secret drug hoarding and drug seeking
- Irritability when cannot obtain dose
- Indifference to dyskinesias, hallucinations, impulse control disorders, or other dopaminergic medication side effects

“Dopamine dysregulation syndrome” (DDS): compulsive overuse of dopaminergic medications

- Is the medication over-use triggered by its pleasurable effects?

  (the “high”)
- Is the medication over-use a protective response against “off” period motor or mood changes?

  (the “low”)

For some, DDS meets criteria for “addiction”:

- Preoccupation with levodopa (craving)
- Impaired control over intake (compulsion)
- Continued over-use despite detrimental effects

“motor fluctuations” versus dopamine dysregulation syndrome

Misdiagnosis is common!

PD patients with compulsive medication over-use often describe there symptoms using “motor terminology”

(e.g. stiffness, inability to move, tremor)

in order to obtain more dopaminergic medication, when in fact they are <u>not</u> experiencing severe “motor” fluctuations, but rather non-motor symptoms: anxiety, panic, dysphoria, agitation, irritability, hypomania.

“dopamine addiction”
Managing “dopamine dysregulation syndrome”

Dopamine dysregulation syndrome frequently goes unrecognized or misdiagnosed.

Risk factors include prior history of substance abuse or psychiatric illness, but patients with DDS represent a diverse cohort, many of whom have no apparent predisposition.

Management:

- Maintain a high index of suspicion in order to make the diagnosis !
- Try to examine patients during their reported “off” spells to see what they are actually experiencing.
- Access to dopaminergic medications must be carefully monitored and appropriately restricted by the physician and the patient’s caregivers.

In summary, physicians treating patients with Parkinson disease must recognize:

- There is a wide range of behavioral disorders related to PD and its treatment
- These “non-motor” problems are quite prevalent in persons with PD
- Unfortunately, some persons develop an “illness identity”, focusing all or their attention on PD, neglecting the positive aspects of their life, and allowing the disorder to dominate every aspect of their daily existence.
- The patient’s “quality of life” often depends more on the recognition and successful management of the behavioral, cognitive, and psychiatric symptoms of PD than on the motor symptoms per se.

COGNITIVE DECLINE and DEMENTIA in PARKINSON DISEASE

Cognitive and behavioral impairments are the major source of disability for some patients with Parkinson disease, and are the leading factors that might require the need for institutional care.

Cognitive efficiency declines with aging

Common complaints in healthy competent older persons:

- Occasional difficulty in promptly recalling names or retrieving words
- Difficulty making or executing plans
- Occasionally misplacing things
- Working at a slower pace
- Difficulty with multi-tasking
- Appropriate mood swings

These symptoms might be more noticeable in persons with Parkinson disease than in age matched controls.

Mild cognitive impairment (MCI) in Parkinson disease- **criteria for diagnosing PD-MCI:**

- Mild cognitive symptoms are reported by the PD patient or the patient's family or symptoms observed by the clinician.
- Deficits at cognitive assessment found in PD-MCI usually affect one or more of these domains:
  - executive function
  - visuo-spatial perception
  - attention / multi-tasking
  - memory loss
- The cognitive symptoms do not significantly interfere with competence or functional independence

Prognosis of mild cognitive impairment (MCI) in Parkinson disease

- MCI is detected in approximately 15% to 30% of PD patients at the time of initial diagnosis.

The prognosis is quite variable:

- The symptoms might remain stable for many years

but

- By 5 years, the symptoms of approximately 50% of the PD-MCI patients will have progressed to be reclassified as "PD-dementia".

however

- About 20% of patients diagnosed with MCI at initial diagnosis of PD are judged to have "normal cognition" 5 years later.

Bradyphrenia (slowness of response)

- Marked slowness of response is common in persons with PD dementia and dementia with Lewy bodies.

However

- Mild bradyphrenia can also occur in persons who do not have dementia or confusion (but the slowness might be misinterpreted and make cognitively intact patients seem impaired).
- Bradyphrenia is very frustrating! patients often feel excluded from conversations or social interactions
- Spouses and friends should allow the patient extra time to respond, and not answer questions for them.

What is “dementia” ?

The meaning of the term “dementia” is often misunderstood: When discussing **“dementia”** with patients or families, explain that dementia is not a specific disease, but is the term used to describe persons who have

significant progressive loss of multiple cognitive functions

(such as executive function, judgment, insight, memory, visual perception, naming, and/or word retrieval)

that significantly impacts their ability to function normally.

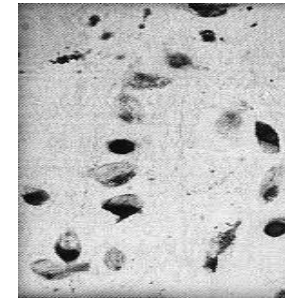
“dementia with Lewy bodies” (DLB) versus **“Parkinson disease dementia” (PDD)**

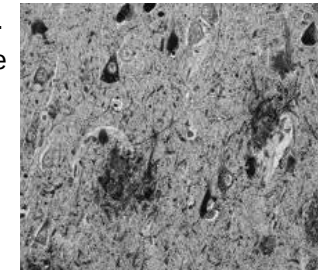
- DLB refers to patients who develop dementia (often with psychotic features) preceding or within a year of onset of parkinsonian motor signs.
- PDD refers to patients who develop significant dementia more than 1 year after the diagnosis of PD.
- There is controversy whether the distinction between DLB and PDD should be maintained or is arbitrary.
- DLB is the second most common cause of degenerative dementia after Alzheimer’s disease.

“dementia with Lewy bodies” (DLB) and
“Parkinson disease dementia” (PDD):

Different illnesses or the same condition ?

- The timing of development of dementia differs, but clinical manifestations are often similar.
- At autopsy, Lewy pathology is seen throughout the brain in both conditions, sometimes also accompanied by “amyloid plaques” and “neurofibrillary tangles” as seen in Alzheimer’s disease.
- Patients with Lewy and Alzheimer pathology are more likely to have the clinical features of both disorders, with greater memory and language problems than usually seen in “pure” Lewy body dementias.





Discussing the diagnosis and prognosis

Be candid but kind when explaining “dementia” to patients and families, emphasizing that this is a non-specific term that encompasses a wide variety of symptoms and impairments with varying degrees of severity.

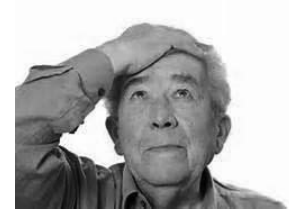
The physician should keep in mind

- “Dementia” is a word with potentially dehumanizing toxic effects and cruel connotations that can rob patients of their humanity and dignity in the eyes of others.
- The word dementia often stigmatizes and isolates patients, making others fearful of dealing with them.
- Although the symptoms and progression might vary from case to case, dementia is a word without hope.
- Do not deny diagnostic information, but do so in words more specific to the patient’s symptoms than just labelling the patient with the word “dementia”.

Arch Neurol 2008; 65: 593-595

What is the prognosis in patients diagnosed with Parkinson disease dementia?

- For some, dementia may be relatively mild and well compensated (especially with help from friends and family), and might remain that way for several years.
- A more aggressive and rapid progression to an advanced state also might occur, but is not inevitable in every case.
- Fluctuations in mental clarity are common: improved thinking can be followed by periods of increased confusion and behavioral changes.
- Unfortunately, by 15 years after diagnosis the vast majority of PD patients will experience some degree of dementia.



Can we predict who is at greater risk for Parkinson disease with dementia?

Patients with:

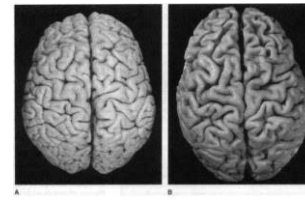
- Older age of onset
- "akinetic rigid" parkinsonism and gait problems without tremor
- Bradyphrenia (slowness of response)
- Depression
- Apathy
- REM sleep behavioral disorder
- APOε4 or GBA mutations

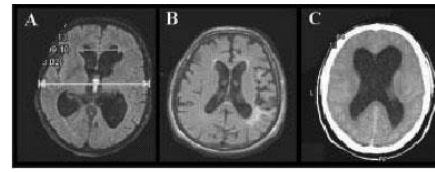
are at higher risk for dementia.

Multiple concomitant medical and degenerative factors (e.g. vascular disease, Alzheimer pathology) are often at play in addition to Lewy pathology when patients with long-standing PD develop dementia.

The differential diagnosis of dementia with "parkinsonian features" includes

- Parkinson disease dementia
- Dementia with Lewy bodies
- Alzheimer's disease with parkinsonism
- Normal pressure hydrocephalus
- Fronto-temporal dementia with parkinsonism
- Progressive supranuclear palsy
- Cortico-basal degeneration
- Multi-infarct dementia ("vascular dementia with parkinsonism")





The one potentially "treatable" condition on this list that should not be over-looked is "normal pressure hydrocephalus".

Defining “dementia with Lewy bodies”

Essential features:

- Difficulties on tests of attention, executive function, and visual perceptual ability may be especially prominent, and occur early in the course of the disease
- Prominent or persistent memory impairment may not necessarily occur in the early stages, but is usually evident with progression

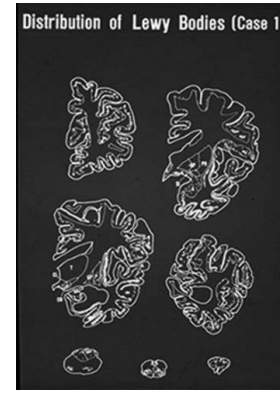
Core clinical features:

- Cognition fluctuates with pronounced variations in attention and alertness
- Recurrent visual hallucinations
- REM sleep behavioral disorder (which usually precedes the cognitive decline)
- One or more cardinal feature of parkinsonism (bradykinesia, rest tremor, and/or rigidity)

Defining “dementia with Lewy bodies”

Supportive clinical features:

- Postural instability and repeated falls
- Autonomic dysfunction (orthostatic hypotension, constipation)
- Syncope or other transient episodes of unresponsiveness
- Hypersomnia
- Systematized delusions
- Apathy, anxiety, depression



Supportive biomarkers:

- Reduced dopamine transporter uptake in the basal ganglia on SPECT or PET scans
- Polysomnographic confirmation of REM sleep behavioral disorder

“dementia with Lewy bodies” can begin with different clinical manifestations, leading to potential diagnostic confusion:

Psychiatric presentation:

- Apathy
- Depression
- Anxiety
- Psychosis (hallucinations, delusions)

Motor symptoms of parkinsonism

Fluctuating cognitive impairment

- Dysexecutive syndrome
- Visuo-perceptual problems
- Bradyphrenia

Autonomic impairment

- Orthostatic hypotension

Sleep disorders

- REM sleep behavioral disorder
- Hypersomnia

Treating motor symptoms in dementia with Lewy bodies

- Parkinsonian motor symptoms are often mild in dementia with Lewy bodies and may not require dopaminergic therapy.
- Patients with DLB have increased susceptibility to medication side effects:
  - Increased psychosis
  - Somnolence
  - Orthostatic hypotension

If treatment is needed, start with very low doses of carbidopa/levodopa and titrate upward cautiously.

- Avoid dopamine agonists or anticholinergic medications.
  (these have a greater propensity than levodopa to trigger hallucinations and psychosis)

Clinical features common to DLB and PDD

- Fluctuations in mental clarity are common, with susceptibility to periods of delirium (often without apparent cause)
- Psychotic features: hallucinations, delusions, paranoia
- Visuo-spatial perceptual problems
- Mood swings
- Apathy
- Bradyphrenia

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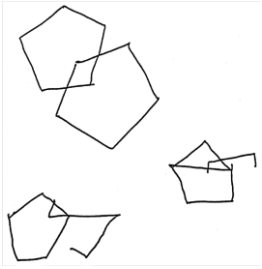


Naming and memory are less affected in DLB and PDD compared to patients with Alzheimer's disease.

(but impaired naming and severe memory loss will be noted in the sizable proportion of DLB and PDD cases that have both Lewy and Alzheimer pathology in the brain).

Potential "triggers" for agitation and delirium in patients with DLB or PDD:

- Fatigue
- Change of routine
- Unfamiliar environment or new caregiver
- Demands to perform beyond limitations
- Excessive stimulation
- Loss of cherished activities
- Boredom / inactivity
- Pain
- Sleep deprivation
- Infection / acute medical illness

However:

mental status often fluctuates in persons with DLB and PDD for no apparent reason

Treating PD dementia (PDD or DLB) with cholinesterase inhibitors

- The “cholinergic deficit” in the brain is greater in PDD and DLB than in persons with Alzheimer’s disease.
- Rivastigmine (and possibly donepezil) can improve global functioning and reduce apathy for some patients with PDD or DLB.
- In some cases, cholinesterase inhibitors might also help reduce hallucinations.
- Nausea and anorexia are a common side effects with oral cholinesterase inhibitors, but are less problematic using transdermal rivastigmine (“rivastigmine patch”):
  Start with 4.6mg/day and increase to 9.5mg/day as tolerated – apply the patch in different locations each day to avoid skin irritation.

Cautions when treating DLB or PDD with cholinesterase inhibitors :

- Increased risk for bradycardia (which can occasionally cause syncope or result in need for a cardiac pacemaker)
- Increased “neurogenic orthostatic hypotension”
- Improved cognition can potentially benefit judgement, and thereby reduce the risk of falling.

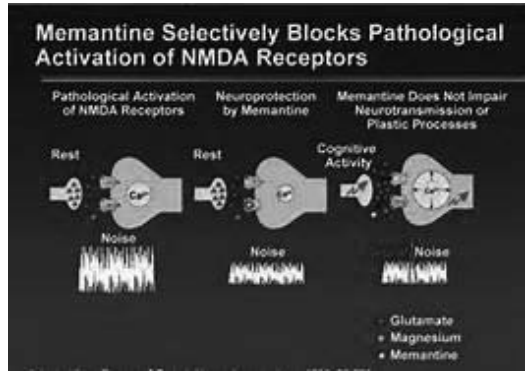
However,

- Orthostatic hypotension and syncope can predispose to falls and hip fractures.
- Nausea and loss of appetite can accentuate weight loss.

Cholinesterase inhibitors are not innocuous:

consequently, if no cognitive or behavioral benefit is seen after an adequate trial of a cholinesterase inhibitor, consider eliminating these medications.

Memantine and PD dementia



- Memantine blocks certain glutamate receptors (NMDA)
- Memantine is often used in combination with cholinesterase inhibitors to treat cognitive impairment in Alzheimer's disease (with limited benefit).
- The value of memantine in improving cognitive function in dementia with Lewy bodies and Parkinson disease dementia is equivocal.
- Concurrent use of memantine and amantadine should be avoided due to the potential for additive side-effects.

Driving and Parkinson disease

There are many issues that might impair driving safety in PD:

- Delayed reaction time
- Excessive daytime sleepiness
- Fluctuating motor symptoms
- Visuo-perceptual problems
- Cognitive impairment
- Impaired judgement
- Concomitant medical problems

A formal driving evaluation by an occupational therapist is necessary if there are questions about the patient's ability to drive safely!

Driving and Parkinson disease

- Loss of driving privileges is a major crisis for many persons, often causing loss of independence and diminished self esteem.
- Patients frequently lack insight, and are unaware or deny that there is any problem with their driving skills.
- Remind patients and families: it is important to stop driving before there is a serious accident rather than afterwards.
- The physician should notify the local Department of Motor Vehicles about persons whose driving safety is in question, but who refuse to voluntarily undergo formal driving evaluation.

AUTONOMIC DYSFUNCTION in PARKINSON DISEASE

The autonomic nervous system is commonly affected in Parkinson disease, resulting in challenges for management of blood pressure, bowel, bladder, and sexual function.

Orthostatic hypotension is common in parkinsonism

Underlying condition	Prevalence of symptomatic Neurogenic OH
Parkinson's disease	**18%**[6]
Multiple system atrophy	**81%**[6]
Pure autonomic failure	**Nearly all**[7]

Causes:

- Parkinson disease related dysautonomia
- Parkinson disease medications (levodopa or dopamine agonists)
- Other medications: diuretics, anti-hypertensives, alpha blockers, phosphodiesterase-5 inhibitors, etc
- Dehydration and inadequate fluid intake! (a common factor)
- "multiple system atrophy" (formerly referred to as "Shy-Drager syndrome")
- Dementia with Lewy bodies

In "neurogenic orthostatic hypotension" the blood pressure drops upon arising **without** significant change in the heart rate (rather than being accompanied by the compensatory tachycardia that would be expected in patients with orthostatic hypotension and intact autonomic function).

Symptoms of orthostatic hypotension:

The "text book" symptoms:

In mild to moderate cases:

A sense of "**lightheadedness**" or "**giddiness**" (pre-syncope): upon arising from a seat or from recumbency or after prolonged standing.

In severe cases:

Fainting ! (**syncope**)

Orthostatic hypotension is often an intermittent phenomenon (for example, noted only after prolonged recumbency, a large meal, exercise, or when the patient is hypovolemic).

In many cases is orthostatic hypotension is asymptomatic.

Symptoms of orthostatic hypotension or "low standing blood pressure" can be vague

Common but "non-specific symptoms":

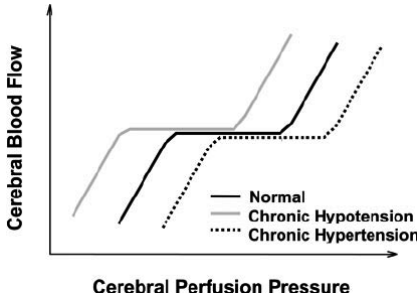
- Weakness / tiredness
- Impaired concentration
- Blurred vision
- Unsteady or vertiginous
- "shakiness" in legs upon arising
- Neck pain ("coat hanger" sign)
- Dyspnea or angina

Check your PD patient's blood pressure and pulse seated and standing at each visit, even if they are asymptomatic.

Dopaminergic therapy and orthostatic hypotension

- Levodopa is a potential contributor to orthostatic hypotension, particularly in patients with concomitant autonomic dysfunction. This is a "short-duration response" after a dose, and seldom persists throughout the day.
- Levodopa induced orthostatic hypotension is most likely to be noted after an early morning dose if the patient arises quickly and is mildly dehydrated.
- The dopamine agonists have a longer half-life, and are more likely to be associated with more significant orthostatic hypotension than levodopa.

How low can blood pressure be before it causes symptoms ?



- Standing blood pressures over 90 systolic are usually asymptomatic: symptoms often are noted in “normal” persons when the blood pressure drops below this level.
- Some Parkinson disease patients with chronic orthostatic hypotension develop compensatory changes in cerebral autoregulation that enable them to tolerate systolic pressures in the 70s without symptoms when standing!

Meals and blood pressure

- Although large meals increase splanchnic blood flow, potentially diverting blood from the heart, this does not have a major effect on blood pressure in healthy people with intact autonomic function
- In people with Parkinson disease and “autonomic dysfunction”, large meals may lower BP by 40mm Hg or more
- Alcohol can accentuate the hypotensive effect of meals

Patients with Parkinson disease are at risk for significant drops in blood pressure and possible syncope after eating very large meals, particularly if accompanied by alcohol consumption.

If the BP is low: "have a big drink of water!"

If a patient has unusually low blood pressure, oral rehydration administered in the office can be very helpful:

- Ingestion of a pint (16 ounces) of water or more over several minutes improves symptoms in many patients with autonomic dysfunction.
- Blood pressure rises within 5-10 minutes of fluid ingestion.
- After oral rehydration, the rise in blood pressure peaks at 20 to 30 minutes, and lasts for over an hour.

Non-pharmacologic management of OH

- Smaller meals
- Increase fluid consumption (water, juices)
- Increase salt consumption (if not contraindicated by congestive heart failure or other medical conditions)
- Decrease alcohol intake
- Sleep or recline with head of bed elevated to reduce the diuresis than occurs when flat
- Exercise leg muscles while in bed prior to standing
- Leg, waist, or abdominal compression devices (e.g. abdominal binder)
- Avoid hot environments (e.g. hot bath, sauna)

Compression garments and elastic abdominal binders:

- Properly fitted waist high compression garments can reduce orthostatic hypotension, but are impractical as they uncomfortable and difficult for most PD patients to put on or take off.
- An elastic abdominal binder is simpler and more convenient to use.
- If placed on while the patient is still recumbent, the abdominal binder might modestly diminish symptoms of orthostatic hypotension upon arising (particularly if the patient drinks 8oz of water or more before standing).
- Abdominal binders will not cause elevation of supine blood pressure.

Exercise and orthostatic hypotension

- Exercise should be strongly encouraged to prevent “deconditioning” which can exacerbate orthostatic hypotension.

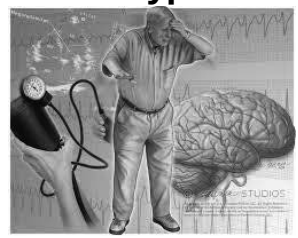
  But:

- The intramuscular vasodilation that accompanies exercise can trigger orthostatic hypotension.

  Therefore:

- Recumbent or seated exercise programs may be preferable.
- The hydrostatic pressure of the water allows exercise in a pool.

Treating orthostatic hypotension in PD



- It is unrealistic to think that the BP can be “normalized” at all times in patients with neurogenic orthostatic hypotension.

However:

- Very modest increases in low BP can often result in dramatic reduction in symptoms (even though the blood pressure remains below what might generally be considered “normal”).

The goal of treatment to reduce the symptoms and morbidity associated with neurogenic orthostatic hypotension without causing severe supine hypertension.

Treating neurogenic orthostatic hypotension

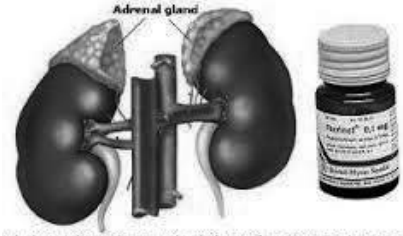
When “non-medicinal” measures fail to help alleviate symptoms of neurogenic orthostatic hypotension consider:

- Fludrocortisone
- Midodrine
- Pyridostigmine
- Droxidopa

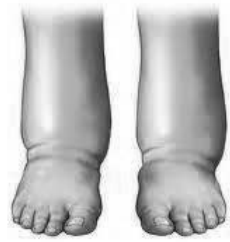
These medications will not be helpful if the patient is hypovolemic or dehydrated!

When using these medications the patient must be frequently monitored for the possibility of severe supine hypertension!

Fludrocortisone



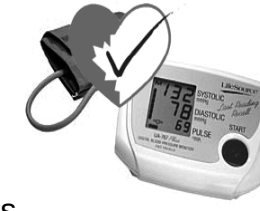
Fludrocortisone is a synthetic form of a natural substance (corticosteroid) secretes by adrenal gland


Edema (swelling) of the ankles and feet

- Fludrocortisone is a mineralocorticoid – the medication increases sodium retention and intravascular volume
- Fluid retention, weight gain, and pedal edema are expected side effects (do not start patients on diuretics to reduce pedal edema associated with fludrocortisone, as this reduces intravascular volume and defeats the purpose of the medication)
- Do not use in patients unable to tolerate an increased sodium and fluid load!
- Monitor for supine hypertension!

Fludrocortisone for orthostatic hypotension

- Fludrocortisone increases potassium and magnesium excretion (levels should be checked 2 weeks after initiating or escalating the dose)
- Replenish potassium if needed: fludrocortisone needs adequate circulating potassium levels to be effective!
- Fludrocortisone also increases calcium excretion and can contribute to osteopenia: adequate calcium and vitamin D supplements are necessary!
- The effect on raising BP is delayed: maximal benefit does not occur for at least 1 week after starting therapy or changing doses
- Doses over 0.2mg/day increase the risk of side effects but are rarely more efficacious
- Monitor for supine hypertension!



Midodrine for orthostatic hypotension

- A selective alpha-1 agonist which constricts venous capacitance beds and arterioles
- Quick onset of action- take only during daytime prior to physical activity: the dose must be titrated carefully:
  2.5mg – 10mg per dose
- Short duration of action (3-4 hours)
- Monitor for supine hypertension

Side effects:

- piloerection, paresthesias
- use with caution in patients with cardiovascular disease
- May decrease urinary outflow in older men
- Does not enter the CNS, and is not a “stimulant”

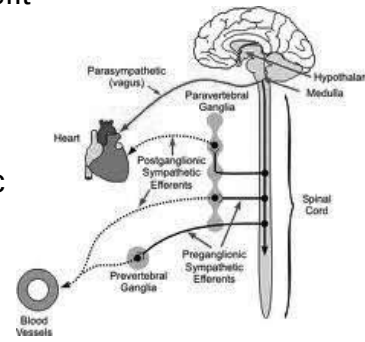
How to use midodrine effectively:

- Check sitting and standing BP at least twice daily: if BP is low only in the morning, doses later in the day may not be necessary
- Check the standing BP and symptoms ~1-2 hours after each dose to determine if dose is adequate
- The effect lasts ~ 3-4 hours: do not take more frequently than this
- Take only when active: do **not** take within 3 hours of bedtime or before long daytime naps (may cause **significant supine hypertension**)
- The starting dose of 2.5mg is usually too low, and most patients will need titration of each dose up to 5 or 7.5 or 10mg
- Avoid “over-shooting” – midodrine can cause very high blood pressures!

Pyridostigmine in neurogenic orthostatic hypotension

Pyridostigmine, the acetyl cholinesterase inhibitor that is used to treat patients with myasthenia gravis also can be of benefit in orthostatic hypotension:

- The pre-ganglionic sympathetic neuron is cholinergic
- Inhibiting acetyl-cholinesterase facilitates transmission of cholinergic impulses across the synaptic cleft
- Traffic in sympathetic ganglia is minimal when supine and greatly increases with standing
- Pyridostigmine can modestly attenuate the orthostatic fall in blood pressure <u>without</u> causing supine hypertension



Pyridostigmine in neurogenic orthostatic hypotension

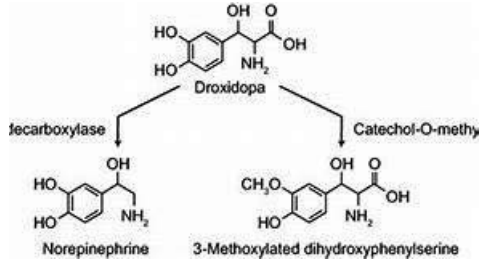
- Start with ¼ of a 60mg tablet (15mg) three times/day
- Increase to ½ tablet (30mg) if well tolerated

Potential side effects:

- Bradycardia
- Bronchospasm
- Abdominal cramps/diarrhea
- Sialorrhea / lacrimation

Pyridostigmine is a useful adjunct to treatment when used in combination with midodrine, droxidopa, or fludrocortisone.

Droxidopa for neurogenic orthostatic hypotension



- Degeneration of post-ganglionic sympathetic neurons in PD reduces norepinephrine levels.
- Droxidopa is an amino acid that is converted both peripherally and centrally to norepinephrine.
- Doses must be titrated according to each patient's response (in clinical trials doses varied from 100 to 600mg tid)
- Droxidopa reduces symptoms (without necessarily "normalizing" blood pressure) for some patients with PD and other disorders associated with neurogenic orthostatic hypotension.

Severe supine hypertension in patients treated for neurogenic orthostatic hypotension

A patient comes to the office with a recumbent blood pressure of 220/110:

- "hold" the next doses of midodrine or droxidopa until the BP comes down
- Have the patient sit up or stand up (which will usually induce a prompt drop in the elevated supine blood pressure)
- A nitro-patch can safely lower the blood pressure acutely
- Re-titrate fludrocortisone, midodrine, and droxidopa doses (recalling that the effects of midodrine and droxidopa are short acting, but fludrocortisone has delayed onset, and its effects can linger for days after the drug is eliminated)

In summary: a practical step-wise approach to neurogenic orthostatic hypotension

- Eliminate meds that cause OH
- Hydrate the patient !!!!
- Upon awakening, the patient should sit up in bed and drink 8-16 ounces of water before arising to walk.
- Wear an abdominal binder (and perhaps support hose) before arising.

If these measures are not adequate and the patient is experiencing symptoms due to orthostatic hypotension:

- Midodrine and/or fludrocortisone and/or pyridostigmine and/or droxidopa can be employed (but must be carefully titrated).

Constipation is a common and annoying problem for many persons with Parkinson disease

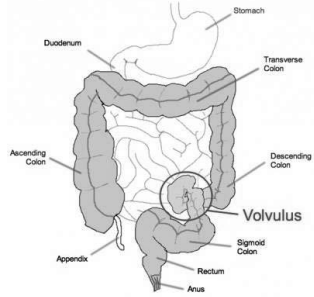
Many contributory factors:

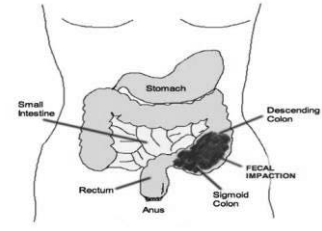
- Dietary:
  inadequate fiber intake
  inadequate fluid intake
- Physical inactivity
- "Autonomic dysfunction"
  loss of neurons accompanied by Lewy pathology in the myenteric plexus
- Impaired contractions of pelvic floor, abdominal, and diaphragmatic muscles due to Parkinson disease
- Medications :
  anticholinergic medications
  anti-parkinson medications

Management of constipation in PD

- Rule out other colonic disorders
- Eliminate constipating medications
- Increase stool bulk by increasing dietary fiber (grains, fruits, psyllium, prunes, vegetables)
- Increased fluid intake! (dehydration can aggravate constipation)
- Stool softeners (not likely to be helpful if the preceding measures are not instituted)
- Stimulant laxatives (senna, bisacodyl)
- Osmotic laxatives (polyethylene glycol)
- Non-irritating suppositories (glycerin)
- Enemas (fleets enema or tap water)
- Increase intestinal fluid secretion (linaclotide)

Complications of constipation in PD



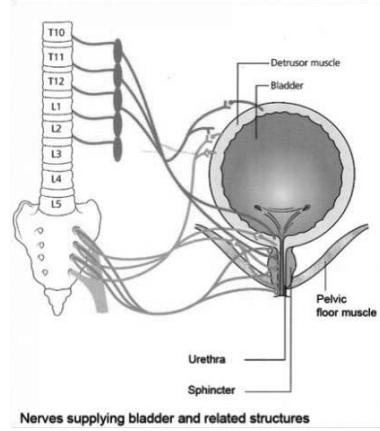


PD patients with constipation are at increased risk for:

- Fecal impaction (sometimes presenting with watery diarrhea around the blocked bowel): patients with fecal impaction should come to the hospital for urgent treatment.
- Bowel enlargement leading to volvulus or megacolon

Pro-active control of constipation can prevent these potentially serious complications.

Urinary symptoms are common in older persons
and may or may not be related to Parkinson disease



Nerves supplying bladder and related structures

"irritative" symptoms:

- Frequency
- Nocturia
- Urgency
- Urge incontinence

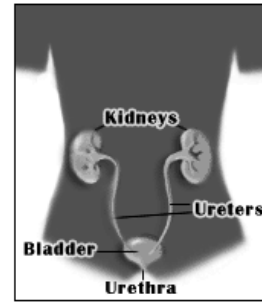
"obstructive" symptoms:

- Hesitancy
- Weak urinary stream
- Over-flow incontinence

An atonic flaccid bladder is unusual in PD and suggests that the patient might have multiple system atrophy.

Urinary symptoms in PD

Urgency, frequency, hesitancy, or incontinence could reflect underlying autonomic dysfunction in PD**,** but should **not** be attributed to PD without also considering other likely factors:



- Medication effects
- prostate problems
- anatomic stress incontinence
- bladder problems
- infection
- constipation

Urologic evaluation is appropriate!

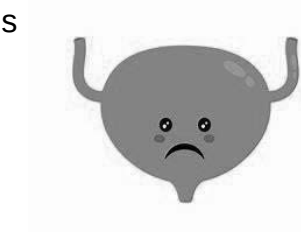
Nocturia in Parkinson disease

- Nocturia disrupts sleep, and is a common annoying problem in older persons with or without Parkinson disease.
- Advise patients to avoid drinking large volumes of liquids after dinner.
- Night time doses of carbidopa/levodopa will sometimes reduce nocturia if the patient is experiencing “wearing off” of levodopa effect during the night.
- Urologic evaluation is indicated before prescribing medications for frequent urination or nocturia.

Urogenital symptoms are likely to be more severe in “multiple system atrophy” (MSA) than PD

Features suggesting MSA rather than PD include:

- Significant neurogenic urinary symptoms preceding or presenting with the parkinsonism
- “erectile dysfunction” preceding or presenting with the parkinsonism
- Urinary incontinence
- Significant post-micturition residual volume (> 100ml)
- Atonic flaccid bladder



Caution when using medications to treat urologic symptoms in Parkinson disease

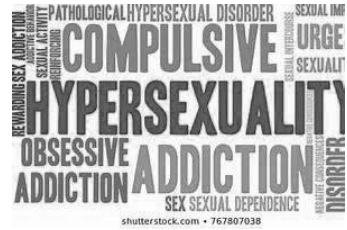
- **Anticholinergic** medications used to treat "over-active" bladder (e.g. oxybutynin) can cause or exacerbate constipation and have cognitive side effects.
- **Alpha-1 adrenergic** medications used to treat urinary hesitancy (e.g. tamsulosin, terazosin) can cause or aggravate orthostatic hypotension.
- **Phosphodiesterase-5** inhibitors used to treat erectile dysfunction (e.g. sildenafil, vardenefil) can cause or exacerbate orthostatic hypotension.

PD patients should be queried about libido and sexual function

Sexual dysfunction is multifactorial:

- Autonomic impairment due to PD
- Immobility related to PD
- Concomitant medical conditions:
  diabetes, vascular disease, hypertension, endocrine disease, urologic disease, arthritis, etc.
- "aging" and physical disability
- "iatrogenic":
  secondary to medications, surgery
- Depression / anxiety

Aberrant sexual behavior in Parkinson disease



Dopaminergic therapies can trigger

- Hypersexuality
- Disinhibition
- Exhibitionism
- Delusions / obsessions

"Impulse control disorders", most commonly aberrant sexuality and pathological gambling, are serious potential complications in patients receiving dopaminergic therapies (particularly dopamine agonists).

Family members must also be regularly queried, as patients will often deny or attempt to hide these problems!

SLEEP PROBLEMS IN PARKINSON DISEASE

Problems affecting sleep and wakefulness are common in Parkinson disease, and have a major impact on patient well-being.

“sleep benefit” in Parkinson disease

- After a good night’s sleep, some PD patients experience improved motor symptoms in the morning despite an entire night without dopaminergic medication:

“sleep benefit”

“When I wake up in the morning I feel like I don’t even have Parkinson disease.”

- Conversely, sleep deprivation can lead to worsening motor function, increased confusion, and increased cognitive impairment

Sleep disorders in Parkinson disease

Over 80% of PD patients have one or more sleep disorders!

These span all aspects of sleep:

- **Falling asleep** (eg depression, RLS, anxiety)
- **Staying asleep** (eg “wearing off”, sleep apnea, nocturia, fragmented sleep)
- **Vivid dreaming** (REM behavioral disorder)
- **Motor activity during sleep** (REM behavioral disorder, restless legs syndrome)
- **Post-sleep behavior** (confusional arousals)
- **Excessive daytime sleepiness** (medication effects, inadequate nocturnal sleep, fragmented sleep, sleep apnea)

Assessing sleep dysfunction in Parkinson disease

- Quality of sleep (is it restful?)
- Difficulty falling asleep?
- Difficulty staying asleep?
- Snoring / sleep apnea ?
- Restless legs syndrome
- Involuntary movements
- Acting out dreams
- Talking or screaming in sleep
- Injurious behaviors
- Excessive daytime sleepiness
- Unexpected “sleep attacks” during the day

Talk to spouse: the patient may be unaware of the problems or unusual behaviors that occur during sleep!

Excessive daytime sleepiness in PD

Many patients with PD experience difficulty maintaining alertness during the day for many potential reasons:

- Is it an effect of anti-PD medication?
- Is it a symptom of the PD itself?
- Is it caused by a nocturnal sleep disorder or inadequate night-time sleep?

Dopamine agonists often induce daytime sleepiness (but this is also a problem for some patients receiving carbidopa/levodopa mono-therapy)

“sleep attacks” (sudden onset of sleep without warning) have occurred in patients on dopamine agonists and have caused serious motor vehicle accidents.

Excessive daytime sleepiness (EDS) in PD

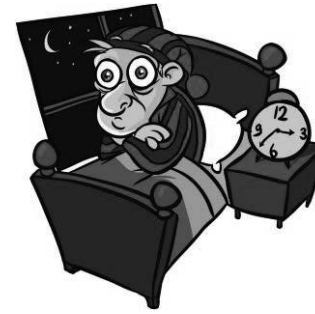
- Screen patients for EDS with a questionnaire such as the “Epworth sleepiness scale”.
- There is an increased frequency of problematic EDS in patients with early untreated PD (12%) compared to controls (5%).
- The incidence of EDS increases further as the disease progresses, affecting 25% by five years after diagnosis.

Treatment:

- Initiate measures to improve nocturnal sleep
- Assess for treatable nocturnal sleep disorders such as sleep apnea
- Stimulant medication (methylphenidate, modafinil, armodafinil) can be helpful for many patients with significant EDS

Insomnia in PD is multifactorial:

- **Age related:**
  - nocturia
  - fragmented sleep
- **Treatment related:**
  - nightmares / vivid dreams
- **Night-time parkinsonian motor problems**
  - rigidity and akinesia
  - tremor
  - akathisia
  - dyskinesia
  - pain and dystonic cramps
- **“Sleep disorders”:**
  - Restless legs syndrome
  - Sleep apnea syndrome
  - REM sleep behavioral disorder
- **Psychiatric**
  - Depression / anxiety



Helpful tips to improve sleep at night

1. Avoid stressful or exciting activities in the evening
2. Do not nap after dinner or take long naps during the day
3. Establish a regular sleep routine, retiring at the same time nightly
4. Do not go to bed too early
5. Use the bedroom for sleeping and not for watching television
6. Sleep in a dark room: use nightshades
7. Do not over-eat in the late evening
8. Avoid caffeine after lunch
9. Do not drink fluids after dinner
10. Avoid clock watching during the night
11. Do not use alcohol as a sleep aid

Sleep fragmentation in Parkinson disease

Falling asleep may not be a problem for some patients. However,

- Staying asleep can be very challenging and is referred to as “sleep fragmentation” or "sleep maintenance insomnia” This affects a substantial proportion of PD patients
- There are many factors that contribute to sleep fragmentation:
  - neurodegeneration of sleep-wake regulatory centers
  - “wearing off” of dopaminergic medication effect
  - depression – anxiety
  - nocturia / “over-active bladder”
  - RLS, PLMS, RBD, sleep apnea, and other sleep disorders

Treating “sleep fragmentation”

- Identify and treat factors contributing to sleep fragmentation:
  - night-time levodopa to prevent “wearing off”
  - treatment of concurrent sleep disorders (sleep apnea, REM sleep behavioral disorder, RLS)
  - treatment of depression / anxiety
  - treatment for nocturia / over-active bladder
- Improve “sleep hygiene”
- Melatonin (3 to 12 mg at bedtime) has modest benefit.
- Benzodiazepines may cause morning sedation, confusion, and impair balance: these commonly prescribed medications should be used with great caution in patients with PD!
- If medication is needed, consider a non-benzodiazepine sedating medication such as trazodone, or mirtazapine.

Insomnia may be due to “wearing off” of levodopa effect in the middle of the night

- If there is difficulty falling asleep, “wearing off” of levodopa effect is sometimes a factor, and a dose of carbidopa/levodopa given at bedtime might be of benefit.
- Frequent awakening / inability to return to sleep in the middle of the night could also be caused by “wearing off” of levodopa effect: in this situation, taking an extra dose of carbidopa/levodopa in the middle of the night can help restore sleep.
- Uninterrupted sleep is beneficial! Patients should not set alarm clocks to awaken themselves from deep sleep for doses of carbidopa/levodopa.

Insomnia and depression in Parkinson disease

If insomnia is related to depression, consider bedtime administration of:

- trazodone or
- mirtazapine

Trazodone (titrated gradually) is a relatively safe night-time sedative for use in older patients.

Mirtazapine is a more effective antidepressant than trazodone, and also has appetite stimulating properties that might useful for patients with weight loss.

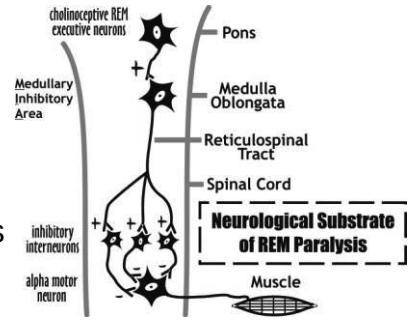
"sundowning" in Parkinson disease

- Lower levodopa doses in the evening may be appropriate for some patients to reduce nocturnal agitation and confusion, but many patients require their usual doses to prevent immobility, tremor, and "wearing off".
- Sleep deprivation is very deleterious, increasing the propensity to psychosis and hallucinations.
- Lack of levodopa during the night sometimes leads to impaired sleep thereby potentially increasing psychiatric symptoms.

"REM sleep behavioral disorder"

During normal REM sleep:

- Dreaming with rapid eye movements
- Signals transmitted from centers in brainstem inhibit motor neurons: the limbs are motionless.



In "REM sleep behavioral disorder":

- REM sleep motor neuron inhibition does **not** occur, and violent dreams can be acted out:

punching, kicking, hitting, talking, yelling, laughing, falling out of bed

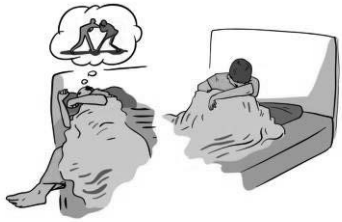
The patient can injure themselves or their bedpartner!

"REM sleep behavioral disorder" (RBD) and Parkinson disease:

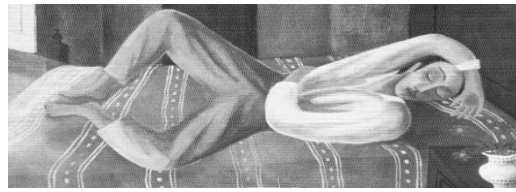
Symptoms of REM sleep behavioral disorder may be noted many years before the motor symptoms of Parkinson disease.
Over 65% of persons who have RBD will eventually develop a "parkinsonian disorder" over the ensuing years:

- Parkinson disease
- Dementia with Lewy bodies
- Multiple system atrophy

are all associated with prodromal REM sleep behavioral disorder.



Diagnosing REM Sleep Behavioral Disorder



The symptoms are not noted every night. However, if during REM sleep the patient has a particularly violent vivid dream:

- Dreams will appear to be acted out
- Movements of limbs and body are associated with aggressive or violent dreams ("fight or flight")
- Potentially injurious sleep behaviors can occur (e.g. hitting bed partner, falling out of bed)
- Talking, yelling, laughing
- Patients (or their spouses) may sustain sleep-related injuries

RBD screening questionnaire

1. Do you experience very vivid dreams?
2. Do you have dreams with aggressive or action-packed content?
3. Do you injure yourself or your bed partner?
4. Do you fall out of bed?
5. Are you known to be talking, shouting, yelling, or swearing during dreams?
6. Are violent fighting movements noted during your sleep?

The history must be obtained from the bed partner, as the patient is most likely unaware of abnormal behaviors that might be occurring during REM sleep.

Definitive diagnosis of RBD requires a polysomnogram demonstrating motor activity during REM sleep.

REM sleep behavioral disorder can be exacerbated by medications

Caused by acute administration:

- SSRIs
- SNRIs
- Tricyclic antidepressants
- Mirtazapine
- Cholinesterase inhibitors
- Beta blockers
- Tramadol
- Caffeine

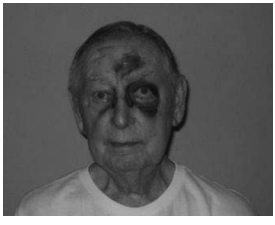
Caused by withdrawal:

- Alcohol
- Benzodiazepines
- Barbiturates
- Meprobamate

Treating REM sleep behavioral disorder

- If possible, avoid medications known to aggravate REM sleep behavioral disorder
- Bedroom safety:

  e.g. remove sharp bedroom furniture, place padding on the floor to prevent injury if falls out of bed
- Co-morbid obstructive sleep apnea should be treated, as this often exacerbates RBD.
- The spouse may need to sleep in a separate bedroom to prevent injury from violent dream enactment behavior.



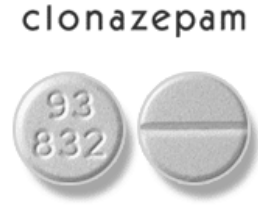
Treatment of REM sleep behavioral disorder (RBD):

Environmental safety interventions are indicated.

Symptomatic episodes of RBD are usually sporadic and infrequent. However, in severe cases or patients with frequent attacks:

- Melatonin (titrating the dose from 3-12mg at bedtime) is sometimes beneficial.
- Clonazepam is the most efficacious treatment for patients experiencing frequent or severe episodes of RBD.

Treatment of REM sleep behavioral disorder: clonazepam:



Use clonazepam with caution!

Clonazepam could exacerbate “sleep apnea”, and cause excessive sedation, confusion, and increase the risk of falls!

Clonazepam helps control both behavioral and dream-disordered components of RBD (start with a low dose and gradually increase if necessary: usual dose 0.25 – 1mg QHS)

Polysomnograms suggest clonazepam acts by suppressing a locomotor center rather than reinstating REM atonia.

Clonazepam remains effective without “tolerance” or withdrawal syndromes over many years of use, but RBD may promptly recur if the medication is discontinued.

CARE-PARTNER ISSUES in PARKINSON DISEASE

The challenges of being a caregiver are often overlooked. The physical and mental health of the caregiver must be considered, as this has a major impact on the quality of life for the entire family unit.

Who has to deal with Parkinson disease?

Parkinson disease does not just affect the patient …

it affects the whole family!

Challenges facing people in coping with a chronic condition

- Learning to accept care and assistance without losing your sense of autonomy or self worth

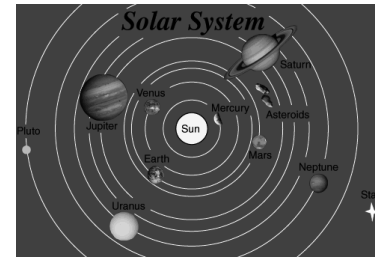
Persons with PD must be reminded:

You are still a “PERSON” and not merely a “PATIENT”

At the same time

- Realizing that everything in the world does not revolve around you and your condition

Patients who refuse help or become self-absorbed create increased stress for care-partners.



“I stayed home and didn’t ask for help because I didn’t want to be a bother”.

Often PD patients who say

“I don’t want to be a bother”

truly become a bother when they complain

“I don’t want to be a bother”

and do not seek or accept help when it is appropriate or necessary to do so. Patients should not be afraid to

ask for or accept help !

However:

“Helping someone often requires doing what they want you to do, not just doing what you want to do for them.”

Caring for people with chronic illness

Patients with chronic conditions are often bombarded by suggestions and advice from well meaning friends, family, social workers, psychologists, or doctors.

People in distress need more than "**advice**", they often need **"help"** !

(The person drowning in this picture does not need someone to recommend swimming lessons, he needs a life preserver!)

Advice that is unrealistic, impractical, or impossible to implement is not helpful, and only serves to increase the patient's frustration and distress.

Non-motor symptoms often cause greater distress for the care-partner than motor symptoms of PD:

Neuro-psychiatric:

- Depression / Anxiety
- Apathy
- Dementia
- Psychosis
- Impulse control disorders

Sleep disturbances

- Frequent nocturnal awakenings
- REM sleep behavioral disorder
- Excessive daytime sleepiness

Autonomic

- Bowel / bladder dysfunction

Care-partners often comment:
"I can deal with his problems walking, but not his confusion or behavior".

Parkinson disease has a major impact on
both the patient and the care-partners:
Who cares about well being of the caregiver?
(the care-partner's health is often neglected)

- The stress of dealing with chronic PD also puts the care-partner's health at risk.
- The well-partner's well-being greatly impacts the care of the PD patient.

Parkinson disease's other victim: the spouse

Typical scenarios:

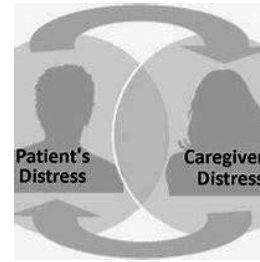
"I knew that hiring someone to help me provide care made sense"

but "I just didn't want to do it."

"No one can provide better care for my loved one than I do."

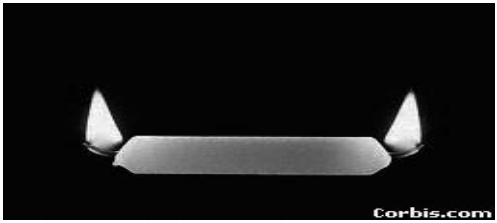
(possibly true, but not helpful in alleviating the strain of being an effective care-partner)

"At first I resented Parkinson disease, but now I also am beginning to resent my spouse!"



“burning the candle at both ends” is unsustainable:

Symptoms of ***CARE-PARTNER BURNOUT***



Denial	Exhaustion
Anger	Sleeplessness
Social withdrawal	Fatigue
Anxiety	Irritability
Depression	Overwhelmed
Guilt - resentment	Health problems

Being a “care-partner” can be overwhelming - remind care-partners:

It’s OK to take care of yourself too !

Every day plan to do something nice for yourself.

Tips for easing the strain of being a care-partner

- Enlisting family members to help on a regular and predictable schedule
- Hiring aides at home for several hours on a regular and predictable basis
- The care-partner should participate in exercise programs on a regular basis
- Participation in education seminars and support groups for care-partners
- Psychological counselling
- Home care
- Enrolling the patient in adult day-care programs can provide much needed respite for the care-partner

Do not drop out of the mainstream of life!

Palliative care in Parkinson disease

- As the burden of chronic disease increases, obtaining “palliative care” is an option that should be considered in PD patients to help optimize treatment
- Palliative care is provided by a team of physicians, nurses, social workers, therapists, and other health professional specialists working together to focus on symptom relief and improving quality of life
- Palliative care is not reserved for end of life, and should not be confused with hospice care that is offered for terminally ill patients

Financial and legal counselling in PD

- Loss of employment, cost of medications, and expensive medical care (e.g. home care or extended care facilities) are potential threats to the family's finances.
- "advanced directives" should be discussed and prepared
- These issues should be considered sooner rather than later in the course of the illness, often requiring consultations with:
  - social worker or
  - financial planner or
  - attorney

Parkinson disease advocacy groups:

American Parkinson's Disease Association:
www.apdaparkinson.org
Davis Phinney Foundation:
www.davisphinneyfoundation. org
Michael J. Fox Foundation for Parkinson's Research:
www.michaeljfox.org
National Parkinson Foundation:
www.parkinson.org
Parkinson's Action Network:
www.parkinsonsaction.org

Clinical trials:
www.clinicaltrials.gov
www.foxtrialfinder.michaeljfox.org

What causes Parkinson disease?

Research has revealed many potential reasons and causes for Parkinson disease.

Will this information eventually lead to a treatment that might prevent or cure Parkinson disease?

There are many factors associated with the risk for developing Parkinson disease (but these are not necessarily related to the cause of Parkinson disease)

Higher risk of PD:

- Older age
- REM behavioral disorder
- Well water or pesticide exposure
- Head injuries
- Toxin exposure
- Constipation
- + family history of PD
- Genetic “risk” factors
- Male gender

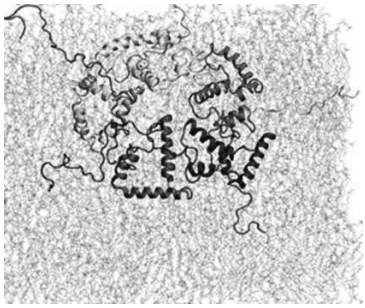
Lower risk of PD:

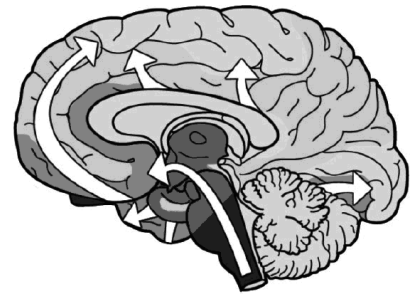
- Younger age
- Smoking
- Regular caffeine intake
- Higher serum urate
- Higher vitamin D levels
- Female gender

Every generation has had its theory of what might cause Parkinson disease:

1880s: **nervous or emotional triggers**
1920s: **brain infection ("post-encephalitic")**
1960s: **lack of dopamine**
1980s: **toxin – environmental exposures**
1990s: **genetic factors**

21st century: PD has many potential **genetic** and **toxic** triggers and causes, but the common feature is the **spread of misfolded proteins** in the nervous system.





Is Parkinson disease genetic?

This simple question has a complex answer:

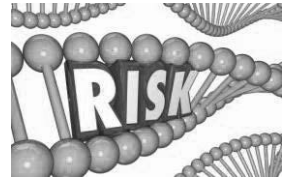
- Mutations in genes for:
  alpha-synuclein (SNCA)
  leucine-rich repeat kinase-2 (LRRK2)
  PTEN-induced kinase-1 (PINK1)
  parkin
  VPS-35
  DJ-1

  have been shown to cause Parkinson disease.

However,

- These mutations are uncommon, and account for fewer than 5% of all PD cases.
- Most cases of PD seem to be sporadic without apparent genetic predisposing factors.

Is Parkinson disease genetic?



This simple question has a complex answer:

- Genome-wide association studies have identified more than 90 "risk genes" that contribute to the overall chance of developing PD, but do not cause PD.

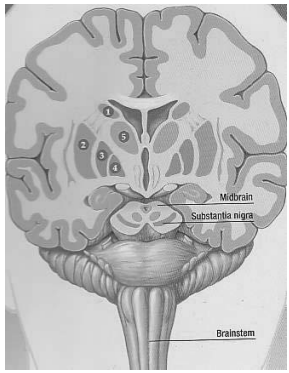
Glucocerebrosidase (GBA) mutations are the most significant "risk genes" for Parkinson disease:

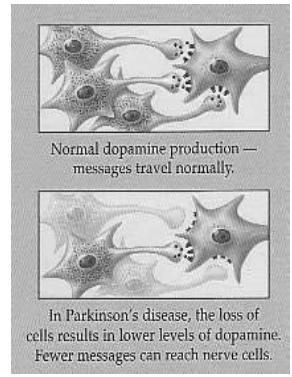
- Heterozygous carriers of some GBA mutations (the autosomal recessive gene responsible for Gaucher's disease) have a several-fold increased risk of developing a parkinsonian syndrome.

Genetic testing in PD
To test or not to test?

- No causative genetic mutation will be found in the majority of PD patients.
- Most causative mutations associated with PD have incomplete penetrance", thereby making the significance of a "positive test" difficult to interpret for an asymptomatic individual.
- Currently there are no "preventive treatments" for asymptomatic genetic carriers.
- Finding a mutation does not change treatment for symptomatic persons at this time.
- Financial cost of testing is significant.
- There is a risk of job discrimination for patient's offspring who are found to have genetic risk factors.
- In the future genetic testing might help improve patient stratification for clinical trials and create genetically informed drug targets

The 20th century model of Parkinson disease as a condition caused by loss of dopaminergic neurons was a major **over simplification:**



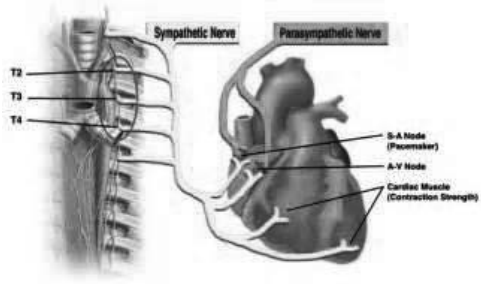


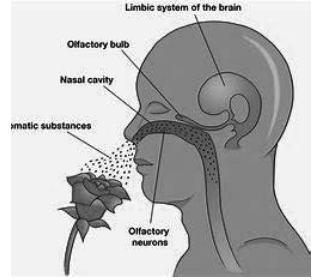
1) Motor problems are <u>not</u> the first symptom of PD !
2) Loss of midbrain dopamine neurons is <u>not</u> the earliest or only abnormality in PD !

"the pre-Parkinson syndrome":

symptoms **preceding** the motor manifestations of Parkinson disease by **<u>many years</u>** include:

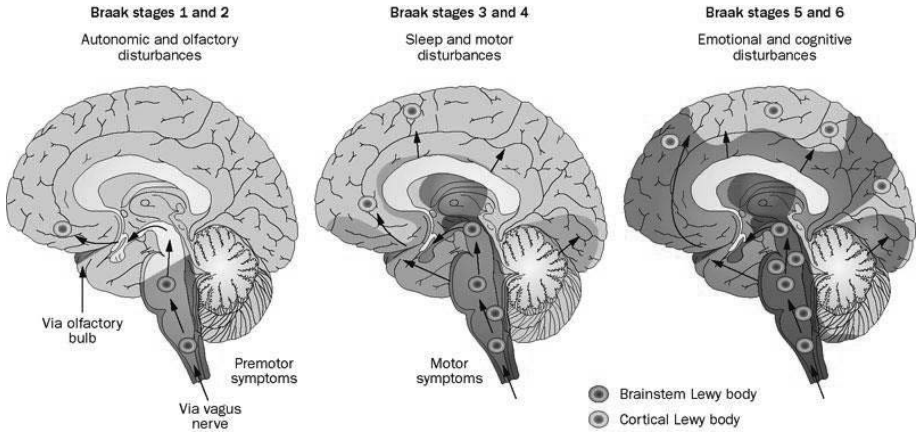
- REM sleep behavioral disorder
- Loss of sense of smell (anosmia)
- Constipation
- Personality and mood changes
- Cardiac sympathetic denervation (which can be demonstrated on MIBG cardiac scanning)



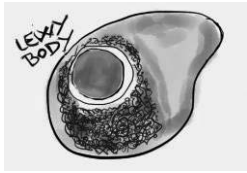


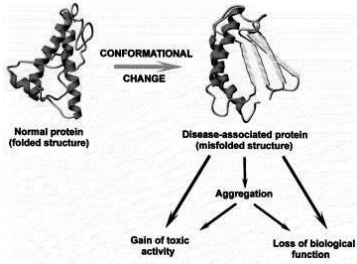
Evolution of Parkinson disease

- The “pre-Parkinson syndrome” suggests initial impairment affecting the olfactory system, autonomic nervous system, gastro-intestinal tract, and lower brainstem.
- Parkinsonian motor signs eventually appear when the midbrain dopaminergic neurons are affected.



α-synuclein and Parkinson disease

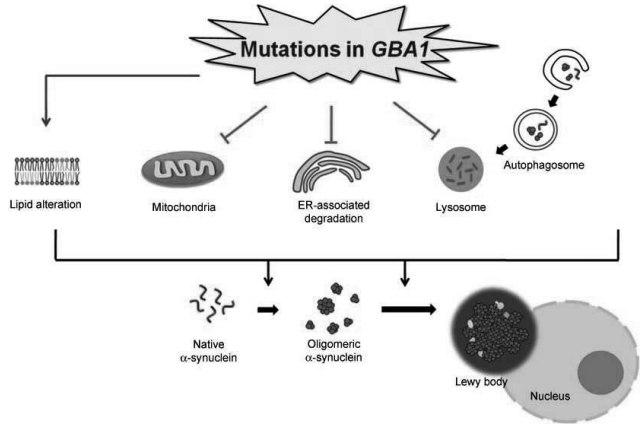




- The protein “α-synuclein” is the major component of Lewy bodies (which are the pathologic hallmark of PD).
- Protein misfolding and deposition can impair normal cell function.
- Multiple lines of evidence suggest that **misfolded α-synuclein** might initially form outside of the brain, and gradually **spread cell-to-cell** (like a prion?) in a deterministic fashion to distant brain regions.

Speculations on how “risk genes” predispose to PD

The increased risk of PD in heterozygous carriers of GBA (glucocerebrosidase) mutations might be related to impaired lysosomal and mitochondrial function that reduces the ability to clear misfolded α-synuclein.



A “cure” for Parkinson disease ?

- The point of convergence triggered by the various causes of Parkinson disease appears to be related to α-synuclein misfolding and spread.
- It is too soon to be certain, but if this is the case, strategies that
  - reduce α synuclein levels,
  - enhance lysosomal or mitochondrial function,
  - prevent protein misfolding,
  - clear misfolded proteins from the brain, or
  - prevent spread of misfolded proteins

might be preventive, slow progression, or lead to a cure for Parkinson disease!

Bibliography

Aarsland D, et al. Cognitive decline in Parkinson disease. Nature Reviews Neurol 2017; 13: 217-231

Ahlskog JE. Cheaper, Simpler, and Better: Tips for Treating Seniors with Parkinson disease. Mayo Clin Proc 2011; 86: 1211-1216

Ahlskog JE. Parkinson disease treatment in hospitals and nursing facilities: Avoiding Pitfalls. Mayo Clin Proc 2014;89: 997-1003

Aurora RN, et al. Best Practice Guide for the Treatment of REM Sleep Behavioral Disorder. J Clin Sleep Med 2010; 6: 85-95

Cummings J, et al. Pimavanserin for Parkinson's Disease Psychosis: a randomized , placebo controlled phase 3 trial. Lancet 2014; 383: 533-540

Deuschl G, et al. A randomized trial of deep brain stimulation for Parkinson's disease.

N Engl J Med 2006; 355: 896-908

Dujardin K, et al. The spectrum of cognitive disorders in Parkinson's disease: a data driven approach. Mov Disord 2013; 28: 183-189

Espay AJ, Lewitt PA, Hauser RA, Merola A, Masellis M, Lang AE. Neurogenic orthostatic hypotension and supine hypertension in Parkinson's disease. Lancet Neurol 2016; 15: 954-966

Espay AJ, Lang AE. Common myths about the use of levodopa in Parkinson's disease: when clinical trials misinform clinical practice. JAMA Neurol 2017; 74: 633-634

Factor SA, et al. Quality improvement in neurology: Parkinson disease update quality measurement set. Neurol 2016: 86: 2278-2283

Factor SA, et al. Recent developments in drug-induced movement disorders: a mixed picture.

Lancet Neurol 2019; 18: 880-890

Friedman JH, Factor SA. Atypical Antipsychotics in the Treatment of Drug-Induced Psychosis in Parkinson's Disease. Mov Disord 2000; !5: 201-211

Goldman JG, et al. Evolution of diagnostic criteria and assessments for Parkinson's disease mild cognitive impairment. Mov Disord 2018; 33: 503-510

Bibliography

Heinzel S, Berg D, Gasser T, et al. Update of the MDS research criteria for prodromal Parkinson's disease. Mov Disord 2019; 34: 1464-1470

LaHue S, Comella C, Tanner CM. The Best Medicine? The Influence of Physical Activity and Inactivity on Parkinson's Disease. Mov Disord 2016; 31: 1444-1454

Lewitt PA. Levodopa for the Treatment of Parkinson's disease N Engl J Med 2008; 359: 2468-2476

Marras C, Lang AE. Changing Concepts in Parkinson Disease. Neurol 2008; 70: 1996-2003

Martinez-Fernandez R, et al. The Hidden Sister of Motor Fluctuations in Parkinson's Disease: A Review on Non-motor Fluctuations. Mov Disord 2016; 31: 1080-1094

Moreau C, Pinto S. Misconceptions about speech impairment in Parkinson's disease. Mov Disord 2019; 34: 1471-1475

McKeith IG, et. al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. Neurology 2017; 89: 88-100.

Nutt JG, Wooten GF. Diagnosis and Initial Management of Parkinson's Disease. N Engl J Med 2005; 353: 1021-1027

Nonnekes J, et al. Unmasking Levodopa Resistance in Parkinson's Disease. Mov Disord 2016; 31: 1602-1609

Olanow CW, et al. Continuous infusion of levodopa-carbidopa gel for patients with advanced Parkinson's disease: a randomized controlled double dummy study. Lancet Neurol 2014;13: 141-149

Olanow W. Levodopa is the best symptomatic treatment for Parkinson's disease: nothing more, nothing less. Mov Disord 2019; 34: 812-815

Palma J-A, Kaufman H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord 2018; 33: 372-390

PD MED collaborative group. Long-term effectiveness of dopamine agonists and MAOb inhibitors compared with levodopa as initial treatment for Parkinson's disease: a large open-label pragmatic randomized trial. Lancet 2014; 384: 1196-1205

Postuma RB, et al. Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's Disease. Mov Disord 2015; 30: 1591-1599

Bibliography

Rizzo G, et al. Accuracy of Clinical Diagnosis of Parkinson Disease. Neurol 2016; 86: 566-576

Robakis D, Fahn S. Defining the role of MAOb inhibitors for Parkinson's Disease. CNS Drugs 2015; 29: 433-431

Seppi K, et al. Update on treatments for nonmotor symptoms of Parkinson's disease – an evidence based medicine review. Mov Disorder 2019; 34: 180-198

Siciliano M, et al. Fatigue in Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2018; 33: 1712-1723

Stowe R, et al. Meta-analysis of comparative efficacy and safety of adjuvant therapy to levodopa in later Parkinson's disease. Mov Disord 2011; 26: 587-598

Thenganatt MA, Jankovic J. Parkinson Disease Subtypes. JAMA Neurol 2014; 71: 494-504

Weintraub D, et al. Initial cognitive changes in Parkinson's disease. Mov Disord 2018; 33: 511-519

Verschuur CVM, et. al. Randomized delayed-start trial of levodopa in Parkinson's disease. N Engl J Med 2019; 380: 315-324

Weiss HD, Marsh L. Impulse control disorders and compulsive behaviors associated with dopaminergic therapies in Parkinson disease. Neurol Clin Practice 2012; 2: 267-274

Weiss HD. Clinical pearls in the evaluation of hyperkinetic movement disorders. Seminars Neurol 2016; 36: 335-341

Weiss HD, Pontone G. Pseudo-syndromes associated with Parkinson disease, dementia, anxiety, and depression. Neurol Clin Practice 2019; 9: 354-359

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