

# An Overview of Parkinson's Disease

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## Cardinal Features

- Parkinsonism
  - ✓ Bradykinesia
  - ✓ Rigidity
  - ✓ Tremor
    - Classically at rest
  - ✓ Postural instability
    - Typically a late symptom

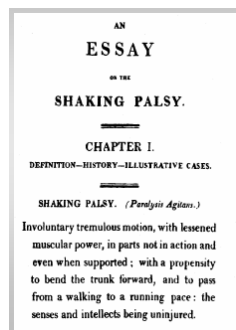


Illustration of Parkinson's Disease by Sir William Richard Gowers 1886.  
[http://commons.wikimedia.org/wiki/File:Dr.\\_William\\_Richard\\_Gowers\\_Parkinson\\_Disease\\_1886.jpg](http://commons.wikimedia.org/wiki/File:Dr._William_Richard_Gowers_Parkinson_Disease_1886.jpg)

- Parkinson's Disease accounts for about 85% of patients with features of parkinsonism - ([wemove.org](http://wemove.org))

## Parkinson's Disease

- In 1817 James Parkinson (1755-1824) described Parkinson's disease.



Parkinson J (1817) An essay on the Shaking palsy. Sherwood, Neely and Jones, London

## Cardinal Features of Parkinsonism - *Bradykinesia*

- Delayed motor initiation
- Slowed voluntary movement
- Rapid fatigue with repetitive movements
- Shuffling gait
- Micrographia
- Decreased dexterity
- Hypomimia (decreased facial expression)
- Hypophonia (low voice volume)

## Cardinal Features of Parkinsonism - *Tremor*

- Classically, a 3-7 Hz rhythmic resting tremor that commonly presents with opposition of forefinger and thumb.
- Hands, legs, lips/chin.
- Rest tremor typically increases with walking and distraction, but decreases with attention or with action.

## Cardinal Features of Parkinsonism - *Postural Instability*

- Loss of postural reflexes
- Retropulsion
- Increased difficulty turning with increased incidence of falls
- Often the most disabling and least responsive to medications
- Not typically present as an early features of Parkinson's disease.

## Cardinal Features of Parkinsonism - *Rigidity*

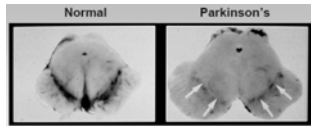
- Involuntary increase in muscle tone
- Lead pipe or cogwheel
- In mild disease, can augment with activation of opposite limb (Froment's maneuver)

## Parkinson's Disease can cause numerous other symptoms including many non-motor

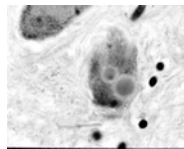
<u>MOTOR</u>		<u>NON-MOTOR</u>
<ul style="list-style-type: none"> <li>• Bradykinesia</li> <li>• Rigidity</li> <li>• Tremor</li> <li>• Postural instability</li> <li>• Micrographia (small writing)</li> <li>• Decreased dexterity</li> <li>• Hypomimia ("Masked Face")</li> <li>• Postural changes</li> <li>• Festination/Freezing of gait</li> <li>• Speech changes</li> <li>• Dysphagia (trouble swallowing)</li> </ul>	} Cardinal Features	<ul style="list-style-type: none"> <li>• Constipation</li> <li>• Anosmia (loss of smell)</li> <li>• Excessive drooling</li> <li>• Gastroesophageal Reflux</li> <li>• Depression/ Anxiety</li> <li>• Cognitive changes/dementia</li> <li>• Sleep disturbance</li> <li>• Seborrheic dermatitis</li> <li>• Bladder urgency/frequency</li> <li>• Sweating spells</li> <li>• Hypotension</li> <li>• Sexual dysfunction</li> </ul>

## Pathological Hallmark of PD

Classic hallmark is degeneration of dopamine neurons from the substantia nigra pars compacta plus intracytoplasmic proteinaceous inclusions (Lewy bodies).



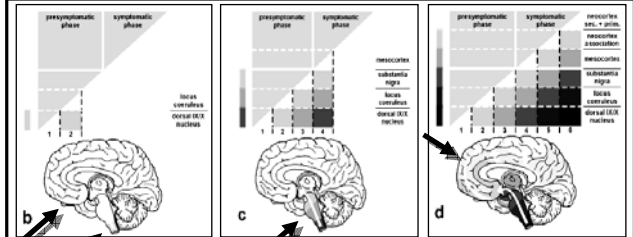
Per decade of life, there is an estimated 9-13% loss of dopamine neurons.



Motor symptoms do not appear until there is a loss of about 70% of dopaminergic neurons from this area.

http://www.srmb.buffalo.edu/juph600/IMC-Pathy2case/2ans18.htm

## Braak Staging of Lewy Bodies



Braak H, et al. J Neurology, 2002;249(suppl 3):1432-1459.

Stage 1 - Lewy bodies (LB) first form within the olfactory bulb and dorsal motor nucleus of the vagal nerve.

Stages 2 and 3 - LB pathology expands into additional brain stem nuclei (e.g., locus coeruleus and substantia nigra).

Stages 5 and 6 - Pathology extends into the cerebral cortex.

More commonly recognized clinical symptoms arise during Stages 4 to 6 when the pathology involves significant regions of the substantia nigra and related brain areas.

## PD Pathology

- PD also associated with extensive pathology in non dopamine cells:
  - ✓ Cholinergic neurons in the nucleus basalis of Meynert and dorsal motor nucleus of vagus
  - ✓ Norepinephrine neurons in the locus coeruleus
  - ✓ Serotonin neurons in the midline raphe
  - ✓ plus many other cells in the cortex, spinal cord, and peripheral autonomic system.
- Pathology in the dorsal motor nucleus and olfactory regions may predate dopaminergic cell loss in the substantia nigra pars compacta.

Forno LS. Neuropathy of Parkinson's Disease. J Neuropathol Exp Neurol 1996;55:259-272.  
Braak H, et al. J Neurology, 2002;249(suppl 3):1432-1459.

## Epidemiology

- As many as 1.5 million people in the US have Parkinson's disease.
- Approximately 60,000 Americans are diagnosed with Parkinson's disease each year.
- Affects 1.5 -2.0 % of people over the age of 60 years.
- Onset of symptoms is typically 60-70 years of age, but up to 15 % of people with PD are diagnosed before the age of 50.
  - ✓ These estimates do not account for cases of PD that are unreported, undiagnosed or misdiagnosed.

National Parkinson's Disease Foundation, Inc. 2007

## Etiology

- The cause is not known, and with most cases of disease being sporadic.
- However, there is a suspected strong link to genetic and environmental factors.
- Risk factors included family history, increasing age, rural living, well water, exposure to pesticides/herbicides, and repeated head injury.
- Some studies have suggested smoking decreases risk of development of Parkinson's disease with no good explanation.

## NINDS Parkinson's Disease Criteria (aka Gilman Criteria)

- **Group A: (at least 2 needed)**
  - ✓ Resting tremor\*
  - ✓ Bradykinesia\*
  - ✓ Rigidity
  - ✓ Asymmetric onset
  - ✓ Postural instability
- **Group B: Suggests alternative diagnosis:**
  - ✓ Early postural instability
  - ✓ Early freezing of gait
  - ✓ Hallucinations
  - ✓ Early dementia
  - ✓ Gaze palsy
  - ✓ Early, severe dysautonomia
  - ✓ Previous condition/drugs known to cause parkinsonism

## Diagnosis of PD

- Parkinson's disease is a clinical diagnosis based on history and exam findings.
- The diagnosis of parkinsonism is classified as:
  - ✓ **Most Likely** - 2 of 4 present cardinal features, with 1 being resting tremor or rigidity.
  - ✓ **Probable** – isolated rest tremor or rigidity alone.
  - ✓ **Possible** - either bradykinesia or postural instability

## Parkinsonism – Differential Diagnosis

- Parkinsonism does not equal Parkinson's disease.
- The differential for parkinsonism include:
  - ✓ **Atypical Parkinsonian Syndromes**
  - ✓ **Secondary Parkinsonism**
    - Vascular
    - Medication induced
    - Infectious
    - Metabolic/Toxic
  - ✓ **Dementia syndromes**
  - ✓ **Other Hereditary degenerative disease**
  - ✓ **Psychogenic**

## Features that may suggest cause of parkinsonism other than Parkinson's disease

- ✓ Symmetric symptoms
- ✓ Early balance/gait trouble or falling
- ✓ Early symptoms of cognitive dysfunction or dementia symptoms that precede onset of features of parkinsonism or within 1 year of motor symptoms.
- ✓ Minimal to no response to levodopa
- ✓ History of exposure to drugs reported to cause parkinsonism
  - Neuroleptics
  - Lithium
  - Depakote
  - Other
- ✓ Stepwise progression or history of CVA
- ✓ Apraxia or alien limb phenomena
- ✓ Vertical gaze palsy
- ✓ Upper motor neuron symptoms on exam

## Atypical Parkinsonian Syndromes

- Progressive Supranuclear Palsy
- Cortico-basalganglionic Degeneration
- Multiple System Atrophy
  - ✓ MSA type P: (Striatonigral Degeneration)
  - ✓ MSA type A: (Shy-Drager Syndrome)
  - ✓ MSA type C: (Olivopontocerebellar Atrophy)

## Testing?

- There is no diagnostic test used to diagnose PD
- Neuroimaging and blood tests are useful to rule out other possible conditions if tremor or history/exam is atypical with features that may suggest a diagnosis other than Parkinson's Disease:
  - ✓ Work up may include:
    - Thyroid profile
    - Ceruloplasmin/Serum copper
    - Brain imaging
    - EMG/NCV
- Confirmation of a diagnosis of Parkinson's disease can be made at autopsy

## Progressive Supranuclear Palsy

- Fairly symmetrical symptoms
- Early onset of gait trouble with falls
- Axial rigidity
- Early dysarthria and gaze impairment
  - ✓ Vertical gaze palsy
- Frontal lobe dementia
- Minimal tremor
- Minimal to no response to levodopa.

## Corticobasal ganglionic Degeneration

- Cortical apraxia and possible alien hand syndrome
- Rigidity and bradykinesia with minimal to no tremor
- Dystonic limb posturing early in disease.
- Very asymmetric
- Minimal to no response to levodopa.

## Secondary Parkinsonism

- Vascular
  - Usually history of acute onset or step wise progression
  - Predominant gait trouble and possible cognitive deficits
  - Supported by brain MRI findings of previous infarcts
- Medication induced
  - ✓ Typically dopamine blocking agents, but others have been more commonly reported as well
 

Metaclopramide	Neuroleptics	Phenothiazines
Reserpine	Butyrophenones	SSRI
Amiodarone	Diltiazem	Valproic acid
Lithium		
- Infectious
  - Postencephalitic, syphilis
- Metabolic/Toxic
  - Hypothyroidism, hepatocerebral degeneration, hypoxia, carbon monoxide, carbon disulphide, cyanide, MPTP.

## Multiple Systems Atrophy

- MSA –type P (Striatonigral Degeneration):
  - ✓ Akinetic rigid parkinsonism with minimal response to levodopa
- MSA – type A (Shy-Drager Syndrome):
  - ✓ Akinetic rigid parkinsonism with early prominent autonomic dysfunction (papillary changes, postural hypotension, urinary incontinence, cardiac arrhythmia, upper airway obstruction)
- MSA – type C (Olivopontocerebellar Atrophy):
  - ✓ Parkinsonism with cerebellar ataxia, abn eye movements, retinal degeneration, pyramidal tract dysfunction. May be familial in an autosomal dominant pattern

## Other causes of Parkinsonism

- Other Hereditary degenerative diseases
  - ✓ Huntington's Disease (juvenile), Wilson's disease, Neuroacanthocytosis
- Dementia syndromes
  - ✓ Significant cognitive issues or dementia prior to or within a year of parkinsonian motor symptoms
    - Diffuse Lewy Body Disease
    - Alzheimer's disease

## Parkinsonian Medications

- Parkinsonian medications increase dopamine activity via precursor levodopa, dopamine agonists or blockage of enzymatic breakdown (MAO-B inhibitors)
  - ✓ Parkinsonian medications can alleviate motor symptoms of bradykinesia, rigidity, and tremor to a certain degree.
  - ✓ Other motor symptoms have mild or no response
  - ✓ Non-motor symptoms rarely benefit from parkinsonian medications

## Levodopa

- Approved by FDA in 1970
- Levodopa is the cornerstone of treatment of Parkinson's Disease motor symptoms, despite all the other available medications!
- Levodopa provides anti-parkinsonian benefit over the entire course of the disease.
- When levodopa is given alone, a large amount is changed to dopamine outside the brain and leads to excessive side effects. Further, only 1-5% of the ingested levodopa is available for the brain.
- Levodopa is combined with a DOPA decarboxylase inhibitor (Carbidopa in the USA) which lessens conversion to dopamine outside the brain making up to 10% available for the brain.
- Taking levodopa with foods rich in protein interferes with absorption.

## PD Medications by Classes

- PD medications are divided in classes based on mechanism of action
  - ✓ Levodopa – Crosses into the brain and is then converted to dopamine
  - ✓ MAO-B Inhibitors – Decreases dopamine breakdown
  - ✓ Dopamine Agonist– Mimics dopamine thus stimulating dopamine receptors so less dopamine is needed
  - ✓ COMT Inhibitors – Prevent the breakdown of levodopa
  - ✓ Anti-cholinergics – Decreases need for dopamine stimulation and mostly helps tremor only
- Potential side effects that can occur with any Parkinsonian medication:
  - ✓ Sleepiness - Nausea, diarrhea, constipation
  - ✓ Vivid dreams - Psychosis/Confusion
  - ✓ Dyskinesia - Lightheadedness

## LEVODOPA

<u>DRUG NAME:</u>	<u>AVAILABLE IN:</u>
Standard carbidopa/levodopa (Sinemet®)	10/100, 25/100, and 25/250 mg
Controlled release carbidopa/levodopa (Sinemet CR®)	25/100 and 50/200 mg
Oral disintegrating tablet carbidopa/levodopa (Parcopa®)	10/100, 25/100, and 25/250 mg

- The dose must be tailored to the individual patient.
- Typical dosing initially 3 or 4 times a day. Less frequent or irregular dosing can lead to early onset of motor complications.

## Carbidopa/levodopa: side effects

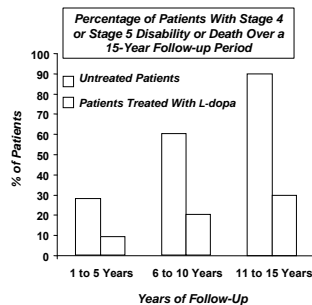
- Common reported potential side effects:
  - ✓ Upset stomach
  - ✓ Nausea/vomiting
  - ✓ Headaches
  - ✓ Visual disturbances
  - ✓ Dizziness
  - ✓ Change in mentation
  - ✓ Sleep disturbances
  - ✓ Motor complications
    - Dyskinesia
    - End of dose wearing off
    - Unpredictable response
- Other serious potential side effects:
  - ✓ Hypotension
  - ✓ Cardiac arrhythmias
  - ✓ Psychosis
  - ✓ Anemia.

## Complications of levodopa

- Levodopa related motor fluctuations typically develop 2-5 years after initiation of levodopa.
  - ✓ Decrease duration of response - "Wearing-off".
  - ✓ Dyskinesia
    - Peak dose dyskinesia
    - Diphasic dyskinesia
    - Off state dyskinesia
    - Dystonic posturing
  - ✓ Inconsistent response with possible no "on".
- Young onset PD patients are more likely to have motor fluctuations given the duration of having symptoms of disease.
- The development of these are thought to be related to:
  - Disease progression
  - Changes in receptors

## Levodopa Slows Overall Clinical Progression of PD

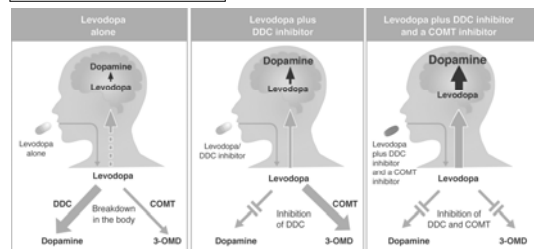
- Rate of clinical progression is slowed
- Life expectancy is substantially increased



## COMT Inhibitors

Enzymes that break down levodopa:  
 1) DDC - DOPA Decarboxylase  
 2) COMT - Catechol-O-methyltransferase

Nutt et al 1994, Gordin et al 2002  
 Stalevo PI, 2003



This medication allows for more levodopa to reach the brain, and prolonged duration of each dose

Schematic of Dual Inhibition of DDC\* and COMT Enzyme Pathways



## Catechol-O-methyltransferase (COMT) INHIBITORS

- Tolcapone (Tasmar®): 100 and 200 mg
  - ✓ Has both central and peripheral action
  - ✓ Dose is 100mg or 200mg dose three times a day
  - ✓ Has a "black box warning" associated with fatal liver failure
  - ✓ Requires monitoring of ALT/AST levels:
    - Prior to starting
    - Every 2-4 weeks for the first 6 months
    - At intervals deemed clinically relevant thereafter
- Entacapone (Comtan®): 200 mg
  - ✓ Mostly peripheral action
  - ✓ 200 mg dose must be taken with levodopa
  - ✓ Increases availability of levodopa in the plasma
  - ✓ Limit 8 a day
- Carbidopa/Levodopa/Entacapone (Stalevo®): 50, 75, 100, 125, 150 and 200
  - ✓ Convenience for patients
  - ✓ Limited to 8 daily doses due to entacapone

## Anticholinergics

DRUG NAME:	AVAILABLE IN:	DOSE RANGE:
<i>Benzotropine (Cogentin®)</i>	0.5, 1, and 2 mg	0.5 – 6 mg/day
<i>Trihexyphenidyl (Artane®)</i>	2, 5 mg and 2mg/5mL elixer	1-15 mg/day
* <i>Diphenhydramine (Benadryl®)</i>	25, 50 mg and 12.5mg/5mL elixer	25-100 mg/day

*\*Secondary action of this medication*

- *These medications can specifically lessen tremor.*
- *Common side effects include confusion, trouble thinking clearly, blurred vision, dry mouth, constipation, and lightheadedness.*

## COMT inhibitors: Side Effects

- **More commonly reported SE:**
  - ✓ Upset stomach
  - ✓ Diarrhea
  - ✓ Discoloration of urine
  - ✓ Sleep disturbance
  - ✓ Dizziness
  - ✓ Headaches
  - ✓ Dyskinesia
  - ✓ Orthostasis

## Amantadine

- This is an antiviral agent approved in 1966, also found to alleviate some motor symptoms of PD in patient in 1969.
- Amantadine (Symmetrel®):
  - ✓ 100 mg pill or 50 mg/ 5 mL solution
  - ✓ Dose: 200-300 mg/day (100 mg PO twice or three times a day. (Max dose 500-600mg/day))
- The exact mechanism of action is unknown; however, it appears to have several properties including:
  - anticholinergic effect
  - enhancing dopamine release
  - anti-glutamatergic (NMDA) effect
- This is one medication that can specifically lessen dyskinesia and smooth out motor fluctuations of levodopa.
- Generally well tolerated
  - Potential Side Effects**
    - Dry mouth
    - Blurred vision
    - Leg swelling
    - Dizziness
    - Depression/Anxiety
    - Hallucinations/Psychosis/Confusion
    - Livedo reticularis
    - Vivid dreams

## Dopamine Agonists

DRUG NAME:	AVAILABLE IN:
Ropinirole (Requip®)	0.25, 0.5, 1, 2, 3, 4, and 5 mg
Pramipexol (Mirapex®)	0.125, 0.25, 0.5, 1, and 1.5 mg
Ropinirole extended release (Requip XL®)	2, 4, and 8 mg
*Bromocriptine (Parlodel®)	2.5, 5, and 10 mg
Apomorphine (Apokyn®) - Injectable only - Used for rescue only.	0.2 mL – 0.6 mL (10 mg/mL)

*\* Not primarily used for PD*

- These activate various dopamine receptors, bypassing degenerating dopamine neurons.
- Longer half-lives than levodopa
- Need to be titrated over several weeks and the response is not as sudden as with levodopa therapy.

## DA agonist: side effects

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>• More commonly reported SE: <ul style="list-style-type: none"> <li>✓ Upset stomach</li> <li>✓ Dizziness</li> <li>✓ Headache</li> <li>✓ Dyskinesia</li> <li>✓ Peripheral edema</li> <li>✓ Confusion</li> <li>✓ Hallucinations/psychosis</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Other adverse reactions that are reported <ul style="list-style-type: none"> <li>✓ Obsessive-compulsive behaviors (like compulsive gambling)</li> <li>✓ Sudden sleep attacks</li> </ul> </li> </ul> |
|---|--|

## Dopamine Agonists

- Can be used alone in early PD or as adjunctive therapy in later PD
- Dopamine agonist often are considered as initial treatment for young-onset patients ( $\leq 50$ ).
  - ✓ It may help prolong the possible onset of levodopa-induced motor fluctuations.
- Dopamine agonists should be used with caution in the elderly patients ( $>70$ ) or anyone with cognitive (thinking) problems at baseline. Concern for higher risk of side effects.

## Apomorphine (Apokyn®)

- It is an older very potent dopamine agonist with rapid onset of action and a very short half life.
- It is only used for rescue during periods of "off" times in between doses of levodopa.
- Administered by subcutaneous injection.
- Associated with significant gastrointestinal upset
  - ✓ Must pretreat with an anti-emetic.
- Other potential side effect:
  - ✓ Lightheadedness (Orthostatic hypotension)
  - ✓ Sleepiness

Apomorphine Hydrochloride injection (Apokyn®)



## Selective MAO-B Inhibitors

DRUG NAME:	AVAILABLE DOSES:	
<b>Selegiline</b> (Eldapryl®)	5 mg	<ul style="list-style-type: none"> <li>• Blocks the enzyme (MAO-B) that breaks down dopamine after it is released from the cell.</li> <li>• This allows for dopamine to be present longer and have a greater effect.</li> <li>• Used for initial therapy or adjunctive therapy.</li> <li>• Possible neuro-protective: Still being investigated</li> </ul>
<b>Zydis Selegiline</b> (Zelpar®)	1.25 mg	
<b>Rasagiline</b> (Azilect®)	0.5 and 1 mg	

## MAO enzyme inhibitor: side effects

- Potential side effects:
  - ✓ Nausea
  - ✓ GI upset
  - ✓ Dizziness
  - ✓ Headaches
  - ✓ Dry mouth
  - ✓ Dyskinesias
  - ✓ Sleep disturbance
  - ✓ Hallucination
  - ✓ Orthostasis
  - ✓ Hypertension

## MAO enzyme inhibitors

- Standard selegiline is dosed twice a day (morning and noon).
- Zelapar and rasagiline are dosed once a day.
- Rasagiline is more selective, more potent, and has less peripheral side effects.
- Zelapar® dissolves rapidly on the tongue, and absorbed into the blood stream bypassing first pass metabolism of the liver. This allows for a lower dose and lessens peripheral side effects.

## Selective MAO-B Inhibitors - Caution

- Hypertensive crisis through tyramine reaction:
  - ✓ AKA: “cheese effect” (red wines, aged foods)
  - ✓ This occurs with doses of MAO-B Inhibitors greater than recommended doses (selectivity is lost)
- Contraindicated with Meperidine (Demerol®)
- Caution advised with the class of anti-depressants “Selective Serotonin Re-uptake Inhibitors”

## Neurosurgical Approach

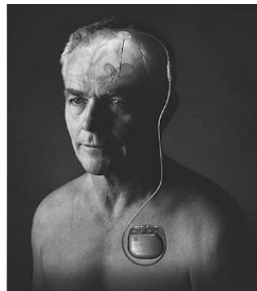
- Deep Brain Stimulation
- Pallidotomy
- Gene Therapy – being investigated
- ?Stem Cell?
- ?Tissue Transplant?

## Neuroprotective Strategies

- Cell death presumed to be from several pathophysiologic factors, including:
  - ✓ Oxidative Stress
  - ✓ Mitochondrial dysfunction
  - ✓ Excitotoxicity
  - ✓ Inflammatory cytokines
  - ✓ Trophic factor deficiency
  - ✓ Signal mediated apoptosis

## Deep Brain Stimulation

- Helps with levodopa responsive symptoms
- Lessens motor complications of levodopa therapy



## Neuroprotective Strategies

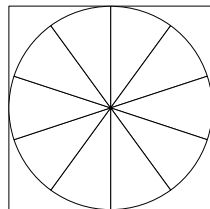
- Neuroprotective?
  - ✓ Vitamin E
  - ✓ CoEnzyme Q10
  - ✓ Vitamin C
  - ✓ Creatine
  - ✓ Anti-inflammatory agents
  - ✓ Exercise

## Tx Non-Motor Symptoms

- Dementia:
  - ✓ Cholinesterase inhibitors (donepezil, rivastigmine, galantamine)
  - ✓ NMDA antagonist (memantine)
- Psychosis
  - ✓ Review medications and check for other health problems
  - ✓ Reduce or wean medications more likely to cause cognitive issues
  - ✓ Quetiapine or Clozapine
- Swallowing / speech
  - ✓ Speech therapy
  - ✓ Daily voice/speech exercises
  - ✓ Modified diet
- Constipation
  - ✓ Fluids, fiber, stool softener
- Bladder dysfunction
  - ✓ Urologist evaluation
  - ✓ Anticholinergic urological agents
- Sexual dysfunction
  - ✓ Hormone levels
  - ✓ Erectile dysfunction medications
- Depression / Anxiety
  - ✓ SSRIs, Bupropion, SNRIs, TCA
- Sleep
  - ✓ Sleep study
  - ✓ Diphenhydramine, Valerian, Melatonin
  - ✓ Sleep hygiene practices
  - ✓ Trazadone, Remeron, Ambien, Rozerem
- Orthostasis
  - ✓ Fluid, salt, compression hoses, raised head of bed.
  - ✓ Lower or wean anti-hypertensives
  - ✓ Midodrine, fludrocortisone

## Strategies in Treatment of disease

- Global Approach
- Education
- Drug treatment to reduce severity of symptoms and improve quality of life
- Adapt lifestyle to maintain function in daily life activities
- Non-pharmacologic interventions are extremely important
  - Daily exercises
  - Physical Therapy
  - Speech Therapy
  - Assistance devices



- Exercise
- Cognition
- Education
- Mood
- Other Health issues
- Sleep
- Nutrition
- Social Activities
- Medication
- Activities