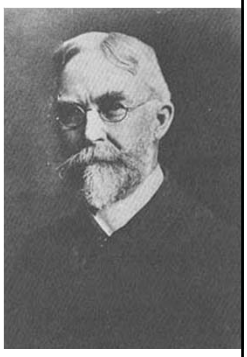
Huntington's & Parkinson's Diseases: Neurologic & Psychiatric Issues

Burton Scott PhD, MD
Duke Movement Disorders Center
Durham, NC

Huntington's Disease

- Typically adult-onset, autosomal dominant disorder characterized by involuntary movements (chorea), dementia, and behavioral changes
- 25,000 affected w/ HD in USA
- Loss of medium spiny neurons from caudate/putamen
- Chm 4p16.3 CAG repeats



George Huntington
1850 - 1916

Huntington G. On chorea. *Med Surg Report* 1872; 26:320

Triad of Symptoms of HD

- HD is a progressive neurodegenerative disease manifested by[1]
  - Motor symptoms
    - Chorea
    - Dystonia, parkinsonism, dysarthria, dysphagia, eye movement abnormalities myoclonus, tics
  - Behavorial symptoms
    - Affective illness, suicide, psychosis, obsessive-compulsive, personality and behavioral changes, sleep disorders
  - Cognitive symptoms
- Chorea is the most visible of the motor symptoms, affecting 90% of patients at some point in their illness[2,3]

1. Marshall FJ. In: Koller R, Watts W, eds. *Movement Disorders: Neurologic Principles and Practice*;2004:589–96.
2. Haddad MS, Cummings JL. *Psychiatr Clin North Am.* 1997;20:791–807.
3. Phillips W, Barker R. ACNR. 2005;5:40-41.

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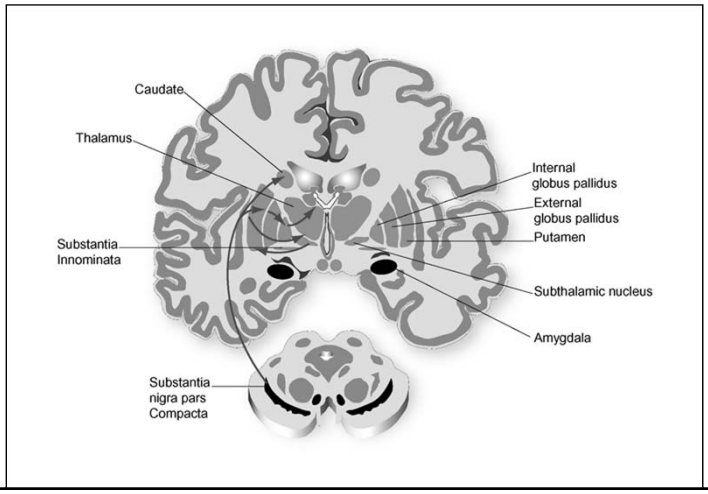
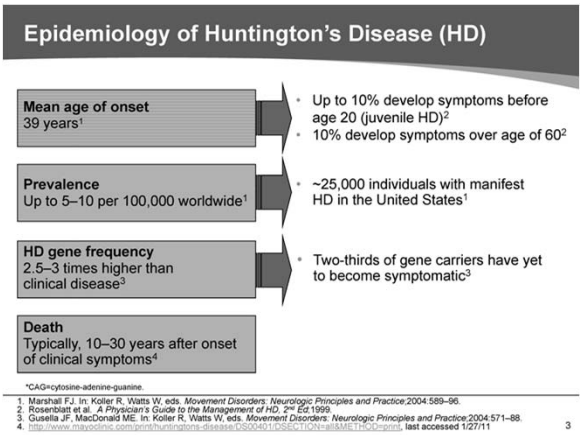
Basal Ganglia

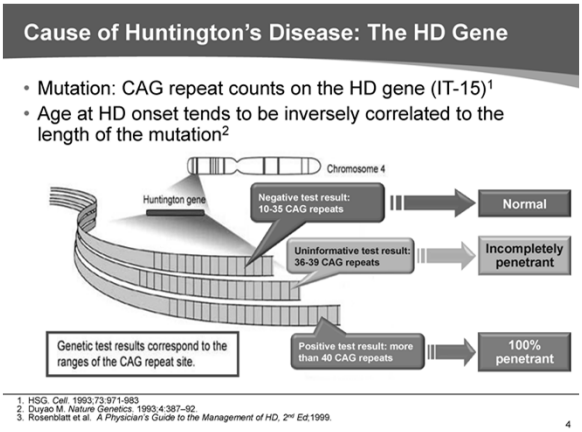
- Huntington's disease
  (loss of medium spiny neurons in striatum:



Epidemiology of Huntington's Disease



Cause of Huntington's disease: The HD gene



Early Huntington's Disease

- 28 yrs old
- 1 yr h/o falls, dropping things
- 6 month h/o mild chorea

Huntington's Disease

- 5 yrs later
- Age 33
- 6 yrs after sx onset

Prodromal Issues in HD

- Impaired perception of time. Frequently late, mis-estimate time needed to complete tasks
- Slowing of processing speed. Ordinary mental tasks more tiring and take longer.
- Impaired determination of emotion from facial expression or verbal intonation
- Impaired smell identification, but detection ok.

Paulsen JS; Curr Neuro Neurosci Rep (2011) 11:474-83

Cognitive Difficulty in HD

- Can occur decades before motor symptoms appear.
- Difficulty learning new things and retrieving previously learned information
- Implicit memory (i.e. skills required to ride a bike, play an instrument, drive a car, perform a task) more compromised than explicit memory (i.e. names, dates)
- Attention deficits
- Impaired executive function
- Impaired communication due to dysarticulation, impaired initiation & comprehension of discourse.
- Can have impairment of one's own actions & feelings

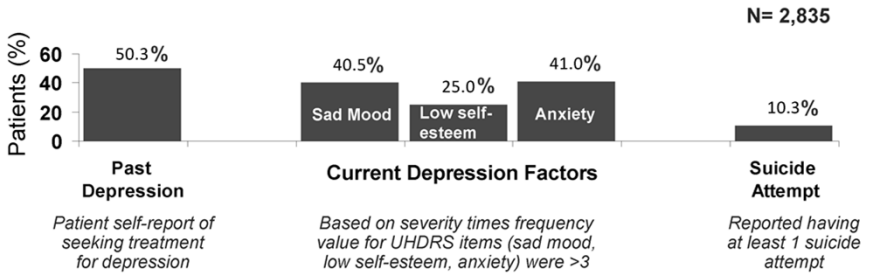
Paulsen JS; Curr Neuro Neurosci Rep (2011) 11:474-83

Mood-Related Symptoms Common in HD

- Presymptomatic carriers of *HTT* mutation: higher psychologic stress, irritability, hostility
- Predict-HD study found depression, hostility,obsessive-compulsiveness, anxiety, interpersonal sensitivity, phobic anxiety, psychoticism in *HTT* mutation carriers 10 yrs before predicted onset of motor sx.
- Depression common; 19% w/ MDD; increased risk of attempted/completed suicide

Acta Psychiatr Scand 105(2002):224-30; Biol Psychiatry 62(2007):1341-6;J Neurol Neurosurg Psychiatry 71(2001):310-4; Neurodegener Dis 8(2011): 483-90; J Med Genet 30(1993):293-5.

Depression is common in HD



→ Participants were diagnosed with definite HD based upon the presence of motor abnormalities observed during the neurological exam of the UHDRS

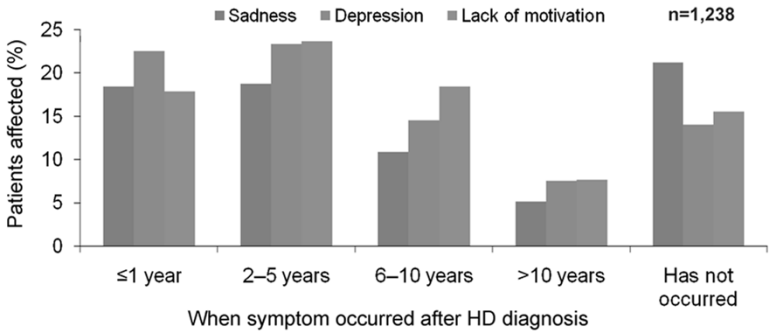
→ The study found rates of depression in HD patients were more than twice that found in the general population

– Depression factors peaked at Stage 2 disease based on TFC

Paulsen JS, et al. *J Neuropsychiatry Clin Neurosci*. 2005;17:496-502.

UHDRS=Unified Huntington's Disease Rating Scale
TFC = Total Functional Capacity

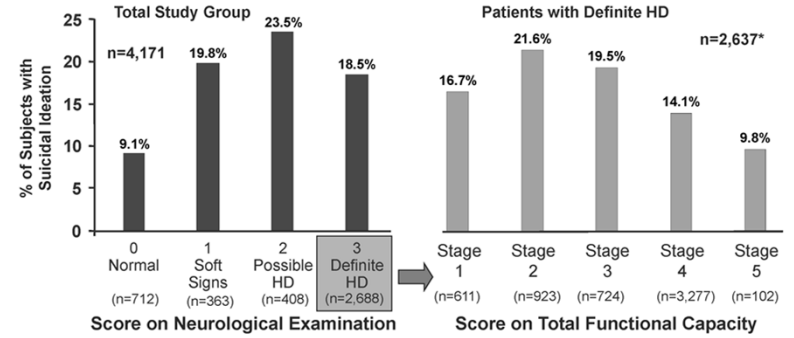
Depression symptoms occur early in HD



- Affected Individual Questionnaire (AQ) completed by close relative of individual with HD
  - Asked if and when a total of 19 physical, emotional, and cognitive signs of HD occurred
- Minimum 6 years from disease onset; mean age at HD onset 41.4 ±10.2 years

Kirkwood S, et al. *Arch Neurol*. 2001;58:273–8

Suicidal Ideation Also Prevalent Pre and Post HD Diagnosis



→ Subjects were from the Huntington Study Group database
→ Used UHDRS motor section; HD diagnosis confidence level rated from 0–3
→ Two scores on neurological exam noted for increase in suicidal ideation
  – Soft neurological signs
  – Possible HD

* With complete data

Paulsen JS, et al. *Am J Psychiatry*. 2005;162(4):725-731.

Cognitive & Behavioral Changes

- Place the greatest burden on HD families
- Most highly associated with functional decline
- Can be predictive of NH placement
- Can be present >15 yrs before motor dx.
- Are highly related to disease specific MRI volume loss

Paulsen JS; Curr Neuro Neurosci Rep (2011) 11:474-83

Medical Treatment of HD

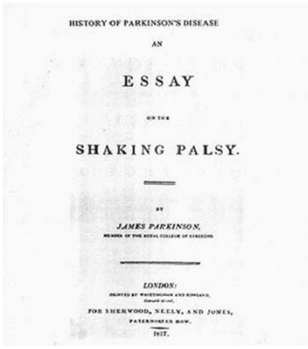
- Motor (chorea): Tetrabenazine, deutetrabenazine
- Behavioral: antidepressants (sertraline & others), antipsychotics (risperidone, aripiprazole & others), anxiolytics (clonazepam)
- Dementia: consider acetylcholinesterase inhibitors off-label such as donepezil, rivastigmine; and also memantine

Summary for HD

- Cognitive (dementia) and Behavioral decline (irritability, compulsiveness, apathy, poor judgement)d are generally more disabling in Huntington's disease than the motor signs and symptoms
- Decline of motor control leads to morbidity due to falls, in addition to weight loss from dysphagia and resulting aspiration and resulting infection.
- HD depletes family resources financially and emotionally

Parkinson's Disease

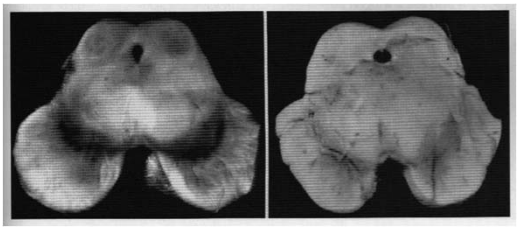
- Dr James Parkinson
- 1755 – 1824
- English physician
- Published "An Essay on the Shaking Palsy" in 1817
- Description of 6 patients


HISTORY OF PARKINSON'S DISEASE
AN
ESSAY
ON THE
SHAKING PALSY.
BY
JAMES PARKINSON,
LONDON:
FOR SHERWOOD, NEELY, AND JONES,
1817.

www.examiner.com; me-jaa.com

Parkinson's Disease: Clinical Features

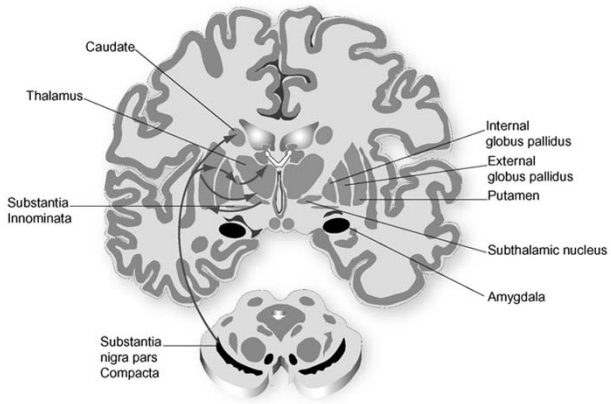
- Chronic neurodegenerative illness caused by loss of dopamine-containing neurons in substantia nigra
- Cardinal signs: Rigidity, bradykinesia, tremor at rest, postural instability
- Other features: Hypomimia, drooling, hypophonia, micrographia, stooped posture, shuffling gait, retropulsion, festination
- Often asymmetric onset

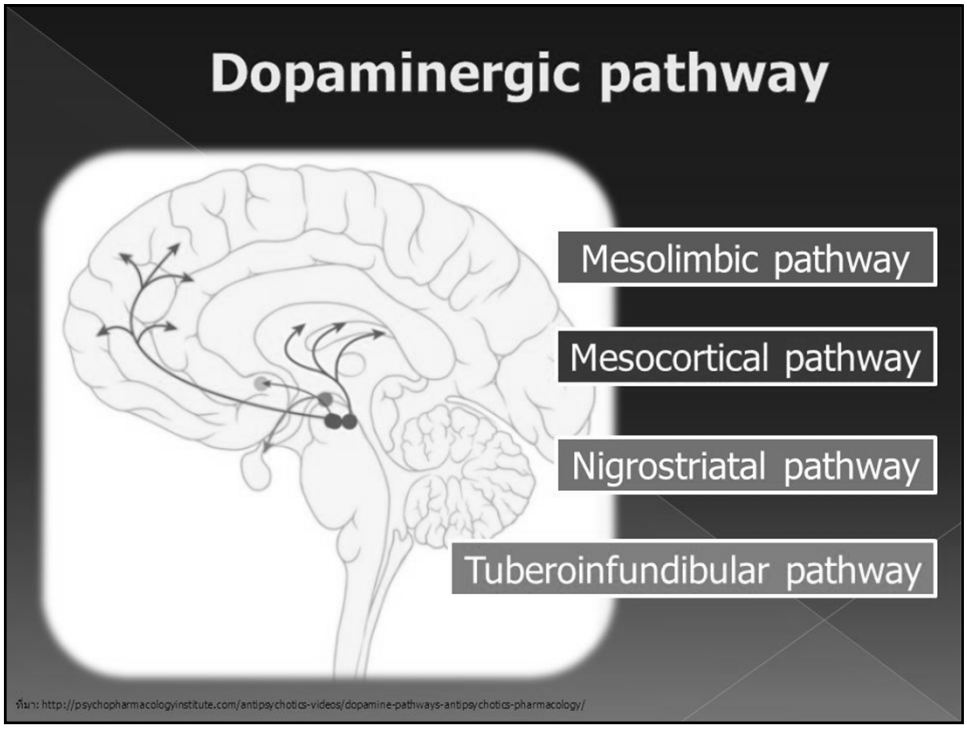


Control Parkinson's disease

Basal Ganglia – Clinical Correlation

- Parkinson's disease (loss of dopaminergic neurons in substantia nigra)




Dopaminergic pathway
Mesolimbic pathway
Mesocortical pathway
Nigrostriatal pathway
Tuberoinfundibular pathway
ที่มา: http://psychopharmacologyinstitute.com/antipsychotics-videos/dopamine-pathways-antipsychotics-pharmacology/


Parkinson's Disease

Symptomatic Treatment of Parkinson's Disease

	Dopamine releaser	
Amantadine	Symmetrel	100-300 mg
	Anticholinergics	
Trihexyphenidyl	Artane	2-10 mg
Benztropine	Cogentin	0.5-8 mg
	MAO-B inhibition	
Selegiline	Eldepryl, Zelopar	5-10 mg, 1.25-2.5mg
Rasagiline	Azilect	0.5-1 mg
	Dopamine agonists	
Bromocriptine	Parlodel	2.5-40 mg
(Pergolide)	(Permax)	(0.25-4.5 mg)
Pramipexole	Mirapex	0.25-4.5 mg
Ropinirole	Requip	2-24 mg
(Rotigotine)	(Neupro)	(2-6 mg/24hrs)

Symptomatic Treatment of PD

	Dopamine precursor	
carbidopa/levodopa	Sinemet regular	10/100, 25/100, 25/250
	Sinemet ext rel	CR25/100, CR50/200
	COMT Inhibitor	
entacapone	Comtan	200-1200
tolcapone	Tasmar	rarely used
	Peripheral Decarboxylase Inhibitor	
carbidopa	Lodosyn	25 – 150 mg
	Combination	
carbidopa/levodopa/entacapone		
	Stalevo	12.5/50/200, 25/100/200
		37.5/150/200

Non-Motor Symptoms in PD include:

- Depression
- Dementia
- Hallucinations
- Sleep difficulty
- Impulse dyscontrol manifested as:
  - pathologic gambling
  - hypersexuality, and
  - other compulsive behaviors.

Neuropsychiatric Symptoms in Early, Untreated PD

- Depression 33%
- Alexithymia 20%
- Anxiety 20%
- Impulsivity 10%

Poletti et al. J Neuropsych Clinc Neurosci 2012; 24:E22-E23.

ICDs in early, untreated PD

Minnesota Impulsive Disorder Interview and South Oaks Gambling Scale

- At least 1 ICD 18.5 %
- Binge eating 7.1 %
- Hobbyism 5.4 %
- Punding 4.8 %
- Hypersexuality 4.2 %
- Buying 3.0 %
- Gambling 1.2 %
- Walkabout 0.6 %

Weintraub et al, Neur, 2013; 80:176-180.

Impulse Control Disorders in Parkinson's Disease

- Compulsive gambling, buying, sexual behaviors, eating, punding
- Failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others (DSM-IV-TR)

Possible ICDs

- Change in personality or behavior
- Increased secrecy
- Increased time at hobbies or work
- Decreased need for sleep, or increased insomnia
- Increased medication intake
- Hoarding medications

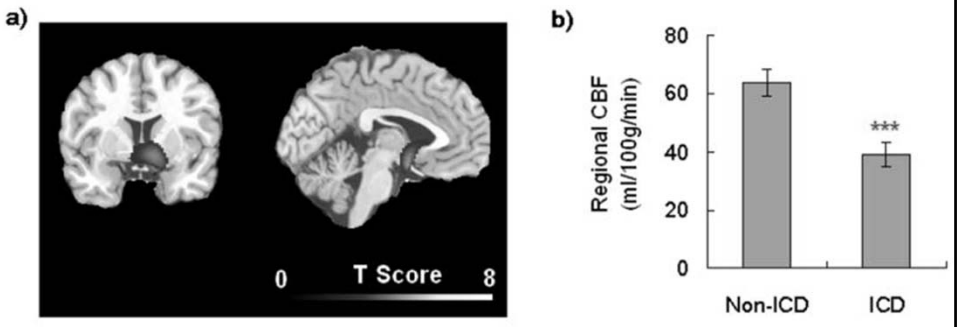
Stacy (2009). Medicine Reports 1:29

Risk Factors for ICD

- PD dx before age 50
- Dx > 5 yrs
- Male
- Hx/o depression, anxiety, bipolar d/o
- Prior drug/etoh abuse, gambling, other addiction
- FHx of mental illness, drug/etoh addiction
- Dyskinesias
- Levodopa or equivalent > 1000 mg/day
- Dopamine agonist use

Stacy (2009). Medicine Reports 1:20

Cerebral Blood Flow in ICD vs non-ICD Parkinson's Disease Pts



Rao et al (2010) Mov Disord 25:1660-1669

Impulse Control Disorder: Cross Dressing

- 82 yo WM with PD. Onset age 70 with decreased dexterity at L hand when typing.
- FHx: Sister with schizophrenia. Mom (d) suicide when pt was age 2. Two children.
- SHx: Flew jets in the military. Married for 55 yrs.
- 73: Urge to cross dress since prostate surgery, w/ incr urges since starting PD meds. Ropin 9 mg, selegiline 5 mg, l-dopa 200 mg
- 73.6: Sees psych for recurr depression. Awakes w/ urge to cross dress.
- 74.1: Psych: urge to wear woman's clothes, ? rel to mother leaving him (suicide) and having 3 step-mothers as child. Stays active to fight cross dressing urges
- Age 82: Still has urges to wear women's undergarments. On l-dopa 900, ropinirole 4, olanzapine 10 (after hospital'n for psychosis, later tapered off), ritalin 10

ICD Case: Compulsive Fishing

- 49 yo WM. Onset PD age 40 w/ sl hand tr, decr L hand dexterity typing.
- FHx: sister bipolar; brother w/ tremor
- SHx: Heavy etoh in college; Navy grad; Married w/2 kids. Executive
- Dxd PD age 41, started pramipexole
- 45: Fishes compulsively "about 1 hr daily", but says, "I don't have to every day". "Not a problem". On L-dopa 800-1000, pram 3; clonaz 2
- 46: Fishing compulsively. Trip to Brazil to fish.
- 47: Eats compulsively. Daytime sleepiness. Rollover MVA, (? sleep driving). Inj knee jumping out of boat. Personality changes. Wife tearful & near to leaving him. Insomnia. Fixates on a topic. Intense. Pressured speech. Decreased insight. Thinks about fishing daily. L-dopa 1200, pram 2, amant 100, rasag 1 mg, modaf 100, amitrip 50

ICD: Fishing

- 48: Compuls eating. "No filter": Says whatever he thinks. Argues, agitated. Fishes compulsively, out 8 PM to 5 AM. On-line poker. Easily distracted. Unable to multitask. Wild dreams. L-dopa 13-1400, entac 1200, pram 2, amant 100, rasag 1. May double meds.
- Then: Wife discovered he spent $100's at a strip club when supposedly out all night fishing. Frequented strip clubs in past, now much more often. Wanted to change, reduce PD meds.
- 48.5: Deep Brain Stim (DBS) surgery
- By age 49: Behavior stabilized. No problems with compulsive urges. Exercising. Doing yard work.
- Taking L-dopa 500 to 600, amantadine 200
- Age 49.5: No compulsive behaviors. Home life stable.

ICD Case: Gambling etc.

- 62 yo WM with PD > 10 yrs.
- Age 54: Rotigotine 13.5 mg patch. Some drowsiness when driving without falling asleep.
- Age 55: Drowsy, not falling asleep driving. Rotigotine 18 mg patch, selegiline 10 mg

Case: Pathologic Gambling

- Age 56.2: Enjoyed "recreational gambling" with losses of $50-100. On PD meds, "addiction" to video poker. Losses of $1-2K over hrs. $150-250K over 2.5-3 yrs, mostly video poker. Made excuses for being late so he could gamble. Read about pathologic gambling & DA use while seeing gambling counselor. He noted increased interest in gambling after starting selegiline.
- H/o cross dressing 2-3/ yr since age 6-7. Not previously interfering with his life. Urges to cross dress became overwhelming since fighting the gambling addiction. Pt & wife separated because she was unable to tolerate his behavior.

Case: Gambling etc.

- Moved into appt. Cross dressed daily after work. Obsessive cleaning. Punding: takes apart lawnmower, cleans it, and puts it back together. Compelled to mow his small yard daily. Emotionally labile. SI, no SA or plan. On selegiline, more aggressive betting. On L-dopa 500 mg, rotigotine 18 mg, selegiline 10 mg.
- Age 56.6: Reunited with his wife of 36 yrs who finds his behavior improved & he is "more like he was years ago".
- No punding. Can concentrate. Still working. Wife working to help w/ debts. Some marital strain due to finances. No cross dressing except briefly a few wkends. No compul gambling since stopped rotigot. L-dopa 400
- Age 59.3: Wife retired. Both home. Financially okay. Reconciled. No ICD. L-dopa 700, amant 200

Impulse Control Disorder (ICD) Treatment

- Recognition of the problem!
- Taper off of stimulants, dopamine agonists
- Treatment with amantadine, antipsychotics
- DBS may permit further reduction of dopaminergic therapy and hence better control of ICD.

Summary for PD

- Both Motor and Non-Motor symptoms are problematic in PD
- Motor symptoms including rigidity, bradykinesias, resting tremor, postural instability
- Non-Motor symptoms include depression, dementia, hallucination, sleep difficulty, and impulse dyscontrol manifested as pathologic gambling, hypersexuality, and other compulsive behaviors.