



# Parkinson Disease--it isn't just a Movement Disorder

Katie Spangler, MD

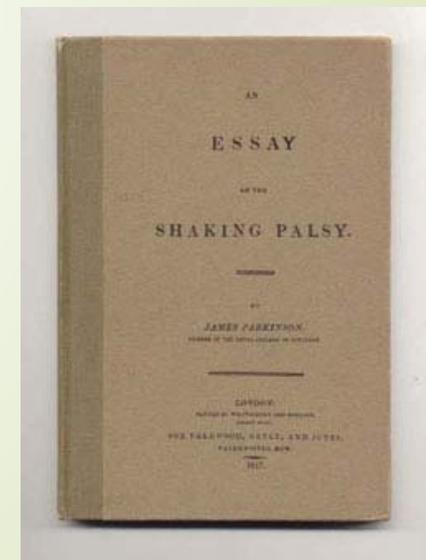
Movement Disorder Neurologist

Marshfield Clinic Wausau/Weston/Minocqua Centers

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# Parkinson disease - history

- ▶ First described in 1817 by James Parkinson
  - ▶ “An Essay on the Shaking Palsy”
- ▶ 1940-1950s surgical options
- ▶ 1960s dopamine found to be depleted in patients
- ▶ 1961-1962 trials of levodopa
- ▶ 1968 levodopa available to use
- ▶ Adjunct medications in the 1970s
- ▶ DBS entertained in 1980s and FDA approved in 1997
- ▶ Dopamine agonists 1998
- ▶ Genetic defects 1990s
- ▶ Other modes of delivery 2007+
  - ▶ Injectable, inhaler, sublingual, infusion
- ▶ High Frequency Focused Ultrasound for tremor 2020
- ▶ Closed-loop DBS 2020





## What Is It?

# Cardinal Motor Symptoms

- Resting Tremor
  - Stiffness (Rigidity)
  - Slowness (Bradykinesia)
  - Gait/Balance (Postural Instability)
- 
- UPDRS-the movement scale used by Parkinson Disease specialists



## Tremor

- Rhythmic shaking of a body part
- Can involve hands, arms, legs, feet, face, head, trunk, chin
- Usually starts out on one side then spread to the other
- Usually starts out with a tremor at rest
- Can start out intermittently
- Worse with stress, anger, anxiety, etc



## Rigidity (Stiffness)

- Stiffness
- Can affect any part of the body
- Test by moving the body part



## Slowness (Bradykinesia)

- ▶ This word means slow (brady) movements (kinesis)
- ▶ Overall speed of accomplishing tasks may be slow
- ▶ Tested by finger tapping, opening and closing of the fist, pronation and supination of the arm and foot tapping



## Gait/Balance

- ▶ Gait – slower, can have shuffling steps
- ▶ Posture - stooped
- ▶ Decreased armswing
- ▶ Later in the disease, may have freezing of gait
- ▶ Balance
- ▶ Ability to right him/herself
- ▶ Tested by the pull test

## Other Symptoms

- Change in handwriting/micrographia
- Softness of the voice (hypophonia), loss of facial expression (hypomimia/masked facies), decreased blinking
- Trouble getting in and out of bed or getting up out of a chair
- Lower extremity cramping, esp. foot often in the morning (“off” dystonia)
- Drooling (siallorhea)

## Micrographia

Mary had a little house in the Radcliffe Infirmary

**January 1995: Before Treatment**

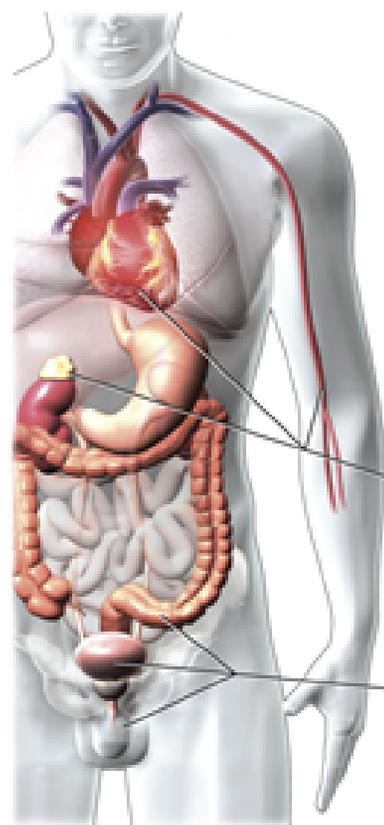
Mary had a little house  
in the Radcliffe Infirmary

**July 1997: After L-Dopa**

Motor	Non-Motor
Tremor	Sleep problems (47%-63%)
Balance problems/Postural Instability	Autonomic Problems: bladder, bowel, sweating, saliva, sexual dysfunction, orthostatic hypotension
Rigidity/Stiffness	Cognition/Thinking (45-60%)
Slowness of Movement/Bradykinesia	Mood (33%-50%) (depression/anxiety/apathy)
	Sensory Symptoms/Pain (63%)
	Fatigue (60+%)
	Psychosis/hallucinations/impulse control disorders/punding
Shulman, et al. 2001	Decrease in sense of smell and taste

# Why Non Motor symptoms?

- ▶ Deposition of alpha-synuclein proteins and Lewy Bodies OUTSIDE the substantia nigra/basal ganglia
  - ▶ Olfactory bulbs (perhaps first site of deposition)
  - ▶ GI tract (maybe this is first site...new evidence)
  - ▶ Salivary glands
  - ▶ Skin/Sweat glands
  - ▶ Retina (abnormal color vision?)
  - ▶ Spinal Cord (bladder?)
  - ▶ Other areas of the brain
    - ▶ Limbic system, prefrontal cortex, hippocampus, amygdala
- ▶ Other Neurotransmitters are involved (not just dopamine)
- ▶ Dopamine neuronal loss affects others....
  - ▶ Serotonin pathways (mood)
  - ▶ Acetylcholine pathways (memory)
  - ▶ Norepinephrine pathways (autonomic symptoms)



**Cognitive impairment**

Subcortical nuclei, limbic regions, cerebral cortex

**Olfactory deficit**

Olfactory bulb, anterior olfactory nucleus, cortical nucleus of amygdala

**Pain**

Spinal cord dorsal horn, brainstem nuclei, thalamus, mesolimbic system

**Visual hallucinations**

Subcortical nuclei (e.g. amygdala), ventral temporal lobe, other cortical regions

**Sleep disorders (RBD, hypersomnolence)**

Brainstem nuclei (PPN, LC, RpN), hypothalamus

**Mood disorders**

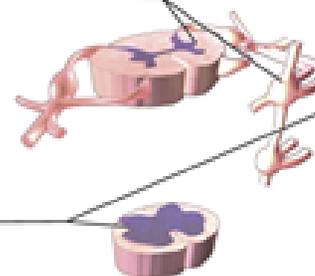
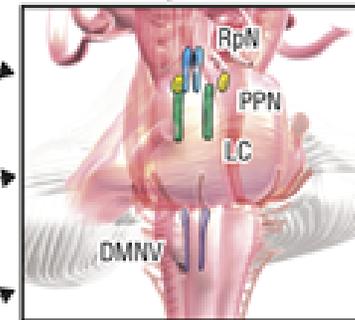
Brainstem nuclei (RpN, LC), mesolimbic dopaminergic system

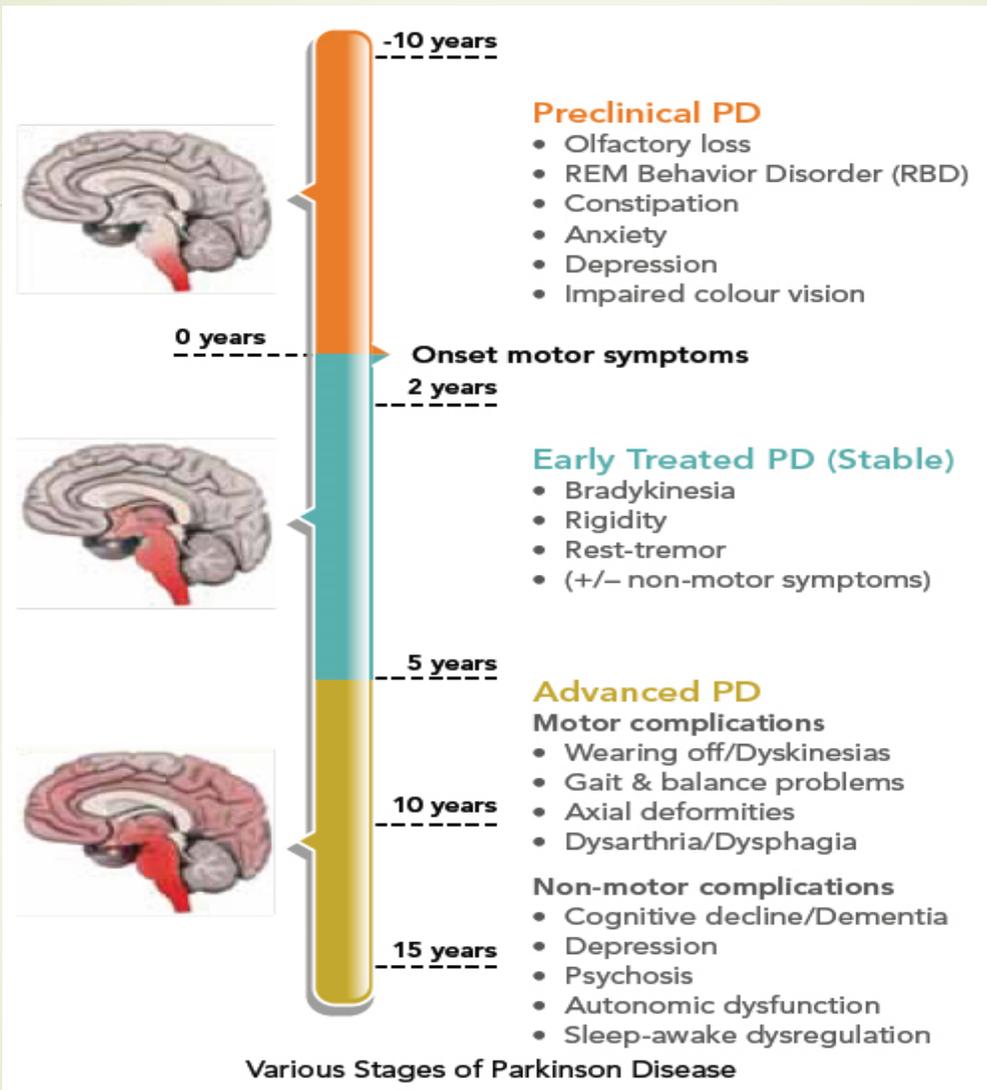
**Orthostasis**

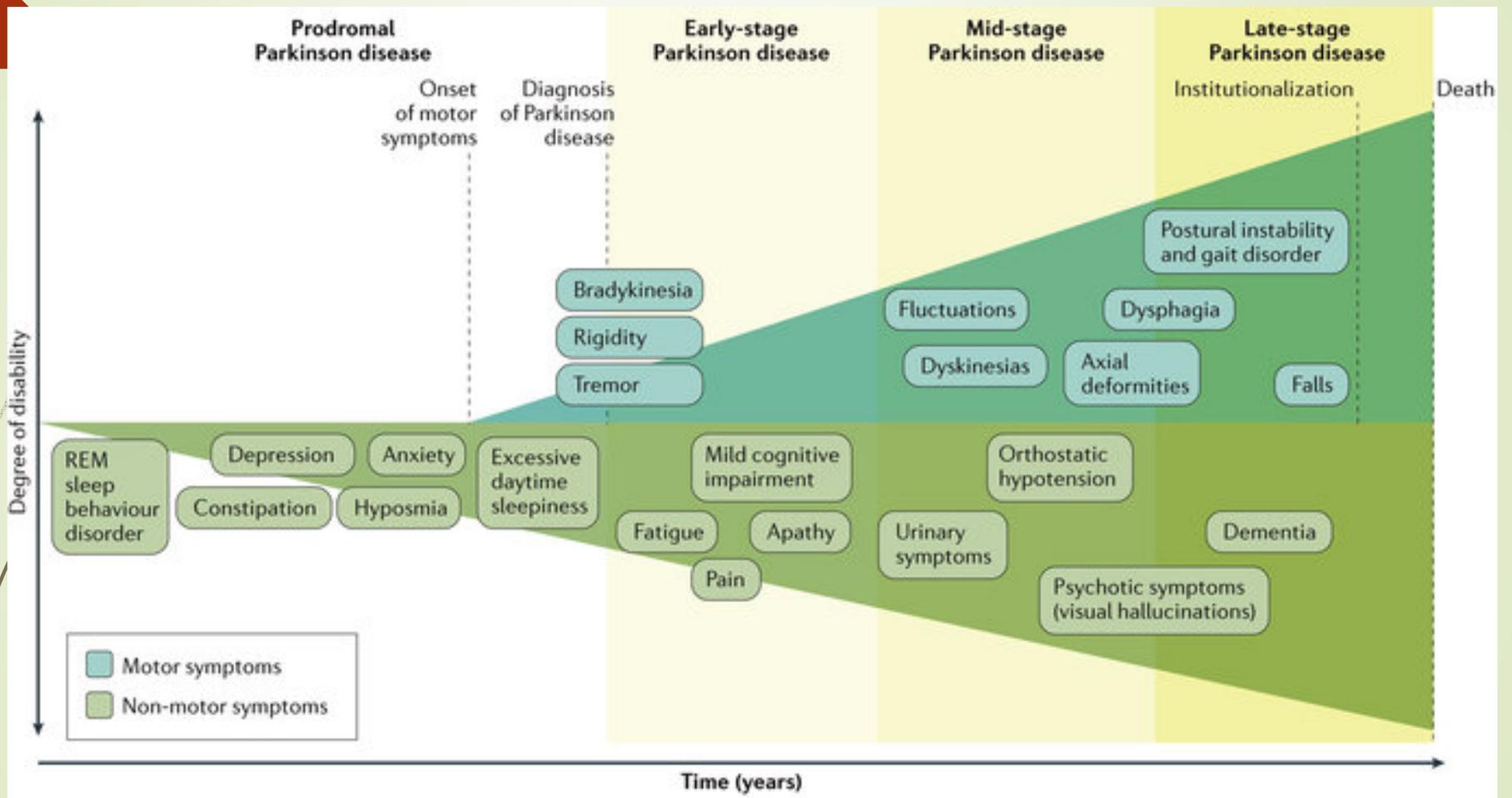
ANS (DMNV, cardiac, vasomotor, spinal cord sympathetic nuclei, sympathetic ganglia, adrenal glands)

**Constipation, urine, and erectile dysfunction**

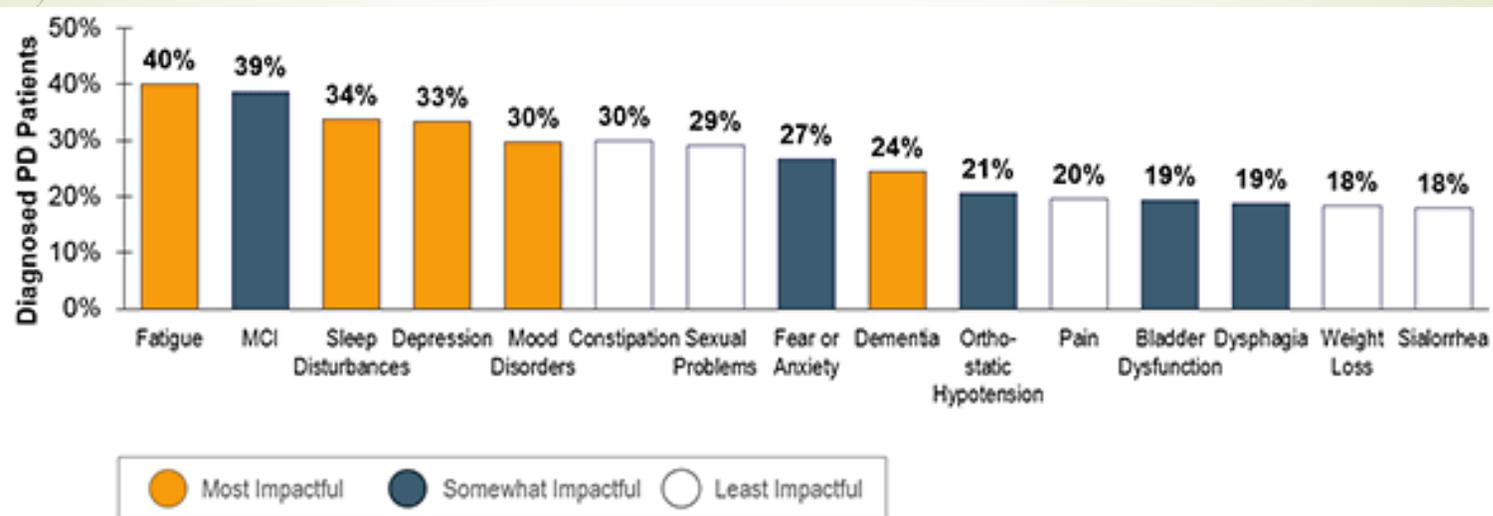
ANS (DMNV, visceral plexus, spinal cord parasympathetic nuclei)







## Non-Motor symptoms can have a larger impact on quality of life than the Motor Symptoms



**PD gives rise to a spectrum of cognitive/neurobehavioral and other non-motor symptoms that highly impact quality of life of patients**

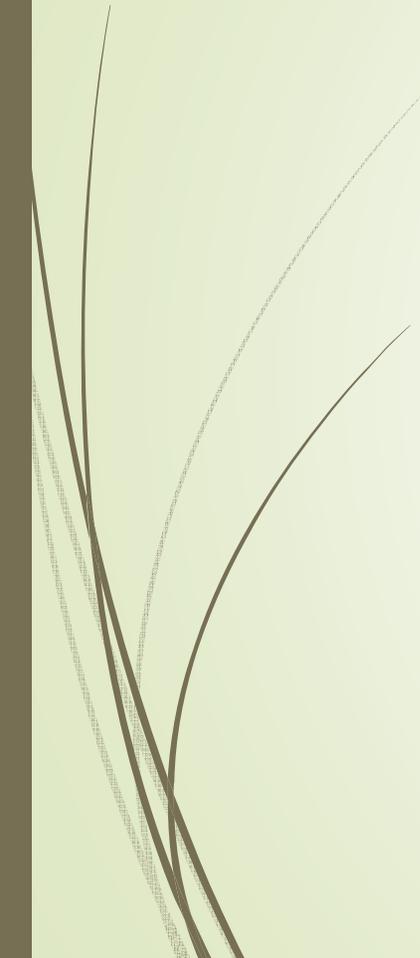
*Health Advances, based on ~200 physicians*



The Michael J. Fox Foundation for Parkinson's Research



# Sleep

- ▶ REM behavior Disorder
  - ▶ Restless Leg Syndrome/Periodic Limb Movements
  - ▶ Sleep Apnea
  - ▶ Excessive daytime sleepiness
    - ▶ Combination?
  - ▶ Sleep attacks
  - ▶ Sleep Fragmentation
  - ▶ Insomnia
  - ▶ Parasomnia
- 



# Autonomic

- ▶ Bladder (hyperactive bladder)
    - ▶ Urinary urgency and frequency
  - ▶ Bowel
    - ▶ Constipation (one of the earliest non-motor)
  - ▶ Sweating
    - ▶ Especially in the hands, feet and head regions
  - ▶ Drooling (siallorhea)
  - ▶ Orthostatic Hypotension
  - ▶ Sexual dysfunction
- 



# NeuroPsychiatric Symptoms “low dopamine state”

Cognitive	Mood (5-20 years before motor)
Slowed processing speed	Anxiety
Executive dysfunction (planning, initiating, organizing)	Depression
Recall	Apathy (15-70%)
Attention/Concentration	Panic Attacks (motor fluctuations?)



# Psychosis- “high dopamine state”

- Hallucinations
  - Visual >>auditory
- Illusions
- Impulse control disorders
- Punding
- Hypomania
- Dopamine Dysregulation

# Hallucinations/Illusions

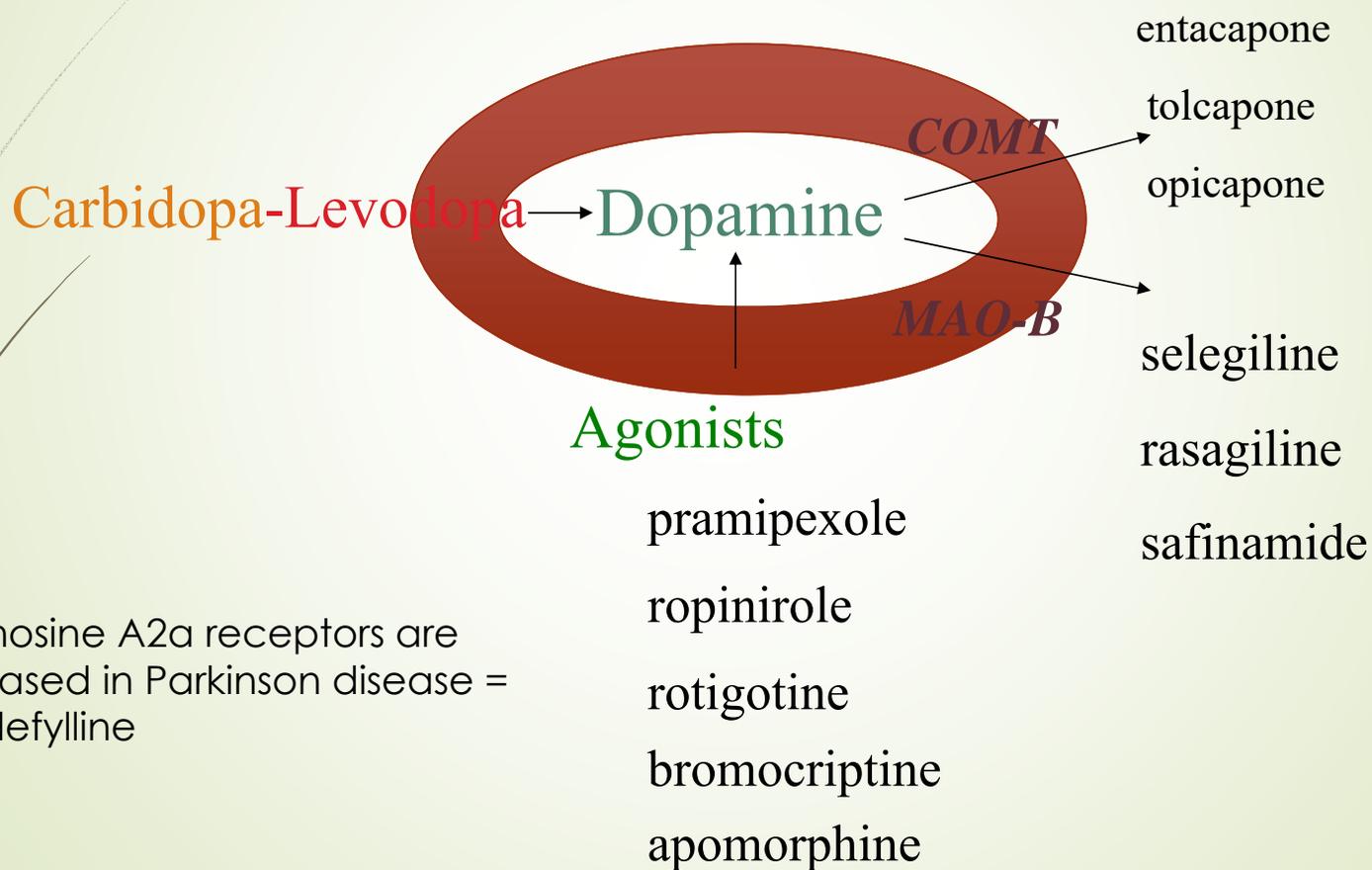
- ▶ Part of Parkinson Disease?
- ▶ Part of Dopamine medication?
- ▶ OR.....
- ▶ Something else?
  - ▶ Infection (bladder), pneumonia, dehydration, other medications?



## Others

- ▶ Pain
  - ▶ Central Pain
  - ▶ Not focal joint pain EXCEPT in dystonia can be focal
- ▶ Smell loss
  - ▶ 5-10 years before motor symptoms
- ▶ Fatigue
  - ▶ Multifactorial?
  - ▶ Motor fluctuations?

# Motor Treatment



# Medications for Motor Symptoms

## 6 classes of medications

### 1. Dopaminergic

- levodopa

Carbidopa/levodopa (Sinemet®); Rytary®, Duopa®, Inbrija®

-dopamine agonists

pramipexole (Mirapex®), ropinirole (Requip®), rotigotine (Neupro®), apomorphine (Apokyn®; Kynmobi®)

### 2. COMT inhibitors

tolcapone, entacapone, Opicapone (Ongentys®)

### 3. MAO-B inhibitors

rasagiline, selegiline, safinamide (Xadago®)

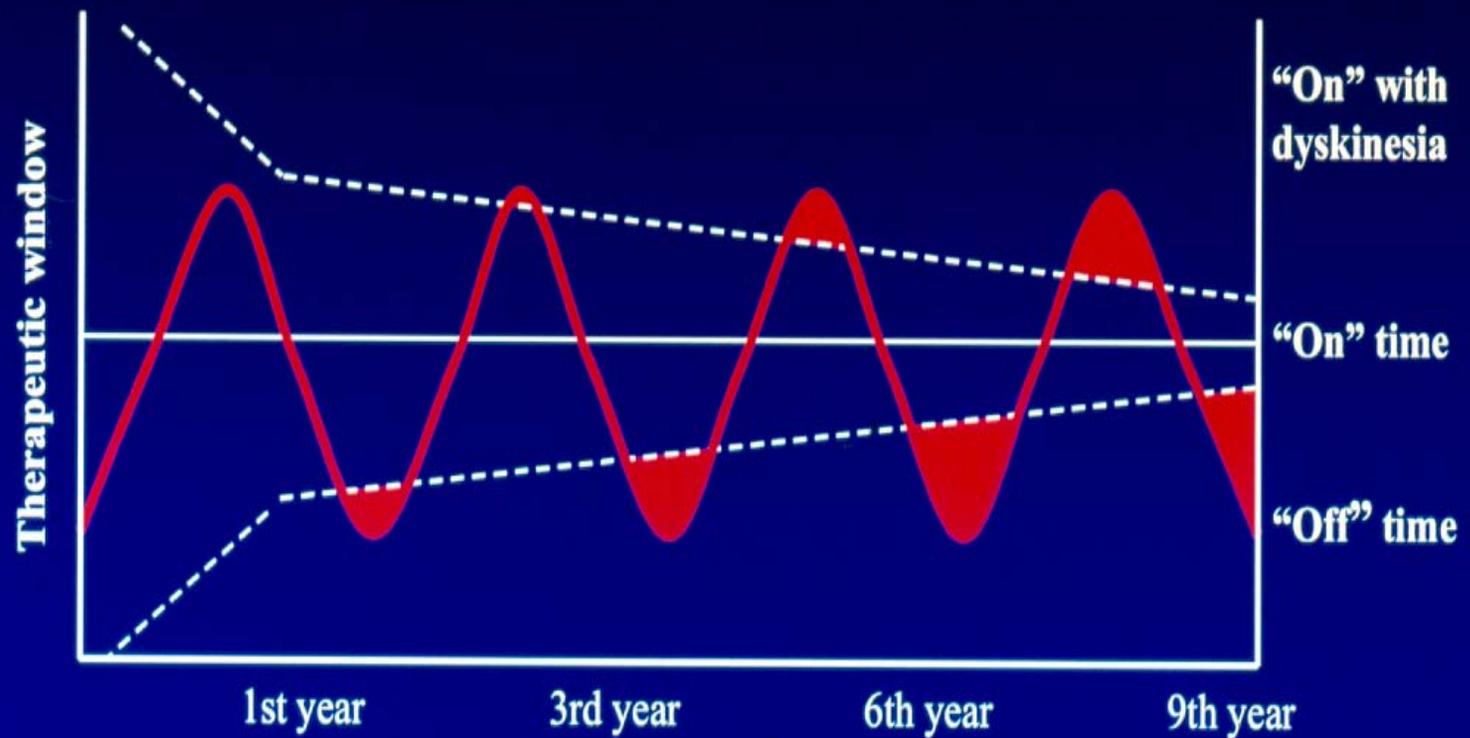
### 4. Anticholinergics

### 5. NMDA Receptor antagonists = Amantadine (Gocovri®)

### 6. Adenosine A<sub>2A</sub> Receptor Antagonists = Istradefylline (Nourianz®)

- 
- We used to think that treatment of motor symptoms have no effect on the non-motor symptoms....BUT DO THEY?!

# The Therapeutic Window Narrows Over Time



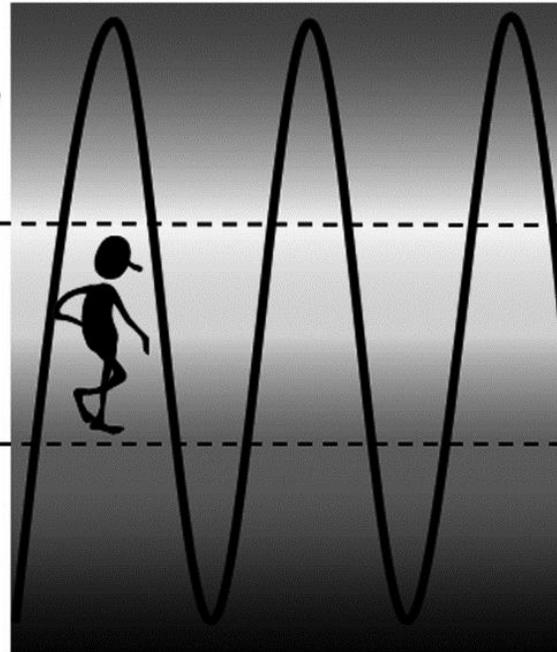
Adapted from Waters Figure 3, reprinted from Stern, 1993.



- MOTOR: Dyskinesias hypotonia.
- LIMBIC: Euphoric, sensation and pleasure seeking, disturbed emotional control, socializing, talkative, joking, teasing, self-confident, maniac.
- COGNITIVE: Disinhibition, cognitive impulsivity, hyperactive, increased creativity, delusions and hallucinations, messy, myopic of the future.



Usual « normal » behaviour  
(motor, emotion, cognition)



- MOTOR: Akinesia, rigidity, tremor.
- LIMBIC: Apathetic, indifferent, feeling dull, tired, withdrawn, dysphoric, sad, vulnerable, lacking self-confidence, suicidal, anxious, having panic attacks, craving for l-dopa.
- COGNITIVE: Bradyphrenia, decrease in verbal fluency.



We have learned that just like motor symptoms can fluctuate...

So can some non-motor symptoms

# Non-motor symptoms reported to manifest as non-motor fluctuations

Table 1. NMS reported to manifest as NMF

Category	Symptom	Distribution in Motor State
Neuropsychiatric	Depression/sadness	OFF > ON
	Apathy	OFF > ON
	Fatigue	OFF > ON
	Anxiety	OFF > ON
	Panic attack	OFF
	Attention problems	OFF > ON
	Forgetfulness	OFF > ON
	Slowness of thinking	OFF > ON
	Mental emptiness	OFF > ON
	Elevated mood	ON > OFF
	Hallucination	OFF < ON
	Mental hyperactivity	OFF < ON
	Mutism	OFF
	Irritability	OFF > ON
	Aggressive behavior	OFF > ON
	Moaning and screaming	OFF
	Confusion	OFF
Drowsiness	OFF	

Autonomic	Light-headedness	OFF > ON
	Limb edema	OFF > ON
	Abdominal pain	OFF
	Abdominal bloating	OFF > ON
	Constipation	OFF > ON
	Nausea	OFF > ON
	Pyrosis	OFF > ON
	Hunger	OFF
	Sexual disorders	OFF > ON
	Drenching sweats	OFF > ON
	Facial flushing	OFF > ON
	Bladder dysfunction	OFF > ON
	Belching	OFF > ON
	Droping	OFF > ON
	Swallowing trouble	OFF > ON
	Chilling	OFF > ON
	Cough	OFF > ON
	Stridor	OFF
	Visual disorder	OFF > ON
Sensory	Diffuse pain	OFF > ON
	Neuralgic pain	OFF > ON
	Dysesthesia	OFF
	Akathisia	OFF > ON
	Burning sensation	OFF > ON
	Sensory dyspnea	OFF
	Restless legs	OFF

Available evidence of the effect of advanced treatments on fluctuating NMS in PD				
Fluctuating NMS	STN-DBS	GPI-DBS	Apomorphine Pump	I-dopa-Carbidopa Pump
<b>Neuropsychiatric</b>				
Depression	+/-	+	+	+
Anxiety	+/-	NA	NA	+
Fatigue	+	NA	+	+
Apathy	+/-	NA	+	+
Attention/cognition	+	NA	+	+
ICD/hyperdopaminergic behaviors	+/-	NA	+	+
Hallucination	+/-	NA	+	+
<b>Autonomic</b>				
Cardiovascular	+	NA	NA	+/-
Constipation	+	NA	+/-	+/-
Drenching sweats	+	NA	+	+
Bladder dysfunction	+	NA	+	+
Swallowing	+/-	NA	NA	NA
Sexual disorders	+	NA	NA	+
<b>Sensory/pain</b>				
Pain	+	+	NA	+
Dysesthesia	NA	+	NA	NA
Restless legs	+/-	NA	NA	NA

Martínez-Fernández, R., Schmitt, E., Martínez-Martin, P. and Krack, P. (2016), A Review On Nonmotor Fluctuations. *Mov Disord.*, 31: 1080-1094. doi: 10.1002/mds.26731



# Treatment of Sleep problems

- ▶ Insomnia
  - ▶ Sleep hygiene
  - ▶ Rotigotine (Neupro™)
- ▶ REM behavior disorder
  - ▶ Combination of pramipexole and clonazepam (being studied)
  - ▶ Clonazepam
  - ▶ Melatonin
  - ▶ Ramelteon (being studied)



# Treatment of Sleep problems

- ▶ Excessive Daytime sleepiness/Sleep Attacks
  - ▶ CPAP (if due to apnea)
  - ▶ Xyrem (Sodium Oxybate)
  - ▶ Reduce medications that could be culprit
- ▶ Overall sleep fragmentation and sleep function
  - ▶ Rotigotine, Levodopa/Carbidopa Intestinal Gel (LCIG)
  - ▶ Treat Bladder issues
- ▶ Fatigue
  - ▶ Stimulants
  - ▶ Rasagiline, dopamine agonists (pramipexole/ropinirole), levodopa



# Treatment of Autonomic symptoms

- ▶ Control Motor fluctuations
- ▶ Bladder/Urgency and Frequency
  - ▶ Solifenacin (Vesicare™); transcutaneous tibial nerve stimulation (being studied)
  - ▶ Botulinum toxin injection
  - ▶ Other anticholinergic medications (Oxybutynin, Detrol)
  - ▶ Mebetriq, might be better due to less side effects (doesn't work on Acetylcholine)
- ▶ Bowel/Constipation
  - ▶ Miralax (only Class I evidence)
  - ▶ High Fiber diet, Adequate fluids and be active!
- ▶ Sweating
  - ▶ Reduce medications that could be the culprit
  - ▶ Botulinum Toxin and oral medications



# Treatment of Autonomic symptoms

- Drooling
  - Medications such as glycopyrolate, scopolamine patch
    - Watch side effects!
  - Botulinum toxin to salivary glands
  - Atropine drops to the tongue
- Orthostatic hypotension
  - Behavioral modifications
    - Drink at least 36-64oz water/day, elevate head of bed, slow to rise
    - Salt food, compressive ABOVE the knees stockings, abdominal binder
  - Fludrocortisone, Midodrine, Droxidopa (Northera™)
- Erectile Dysfunction
  - Cialis, Viagra, Levitra



# Treatment of Mood and Apathy

- ▶ Control the motor fluctuations (see earlier slides)
  - ▶ Increasing the dopamine (Levodopa/Carbidopa intestinal gel; apomorphine)
  - ▶ Rasagiline and selegiline both noted to reduce depression
- ▶ Anti-anxiety or anti-depression medications
  - ▶ Atomoxetine (being studied)
- ▶ Cognitive Behavioral Therapy
- ▶ Exercise and stay active (physically and socially)
- ▶ Apathy –
  - ▶ treat with motor medications (dopamine) more than depression medications
  - ▶ Keep routine/schedule
  - ▶ Piribedil (being studied)

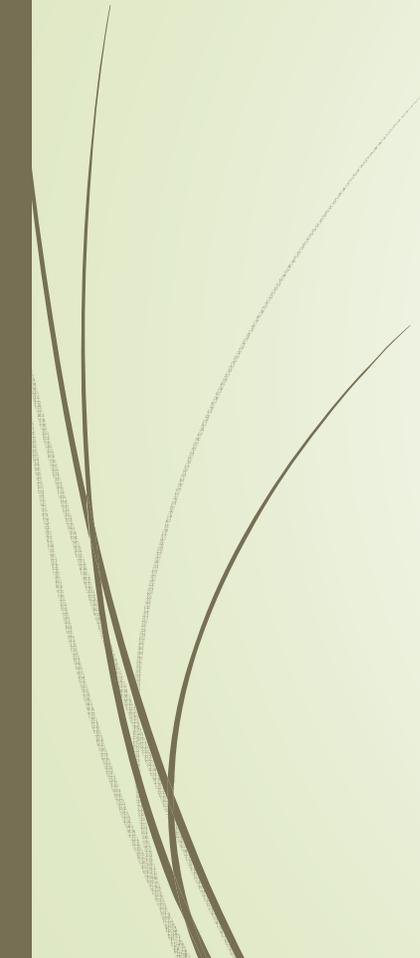


# Treatment of Cognition

- Control motor fluctuations
- Medications (Cognitive Stabilizers)
  - Rivastigmine\*\*, Donepezil, Galantamine, Memantine
- Cognitive Therapy
- Social Interaction
- Physical Exercise
- Mental Exercise (puzzles, etc)



# Treatment of Psychosis

- ▶ Get rid of possible culprit (medications?)
    - ▶ Impulse control, punding, dopamine dysregulation
  - ▶ Check for infection, medical issues going on
    - ▶ Especially if acute onset of hallucinations/confusion
  - ▶ Dopamine blockers
    - ▶ Most can worsen the symptoms of Parkinson disease so be careful!
    - ▶ EXCEPT quetiapine and clozapine
    - ▶ Donepezil (being studied)
    - ▶ Pimavanserin (Nuplazid™) (approved 5/2016)
  - ▶ Redirection, agreement, console, safety
- 

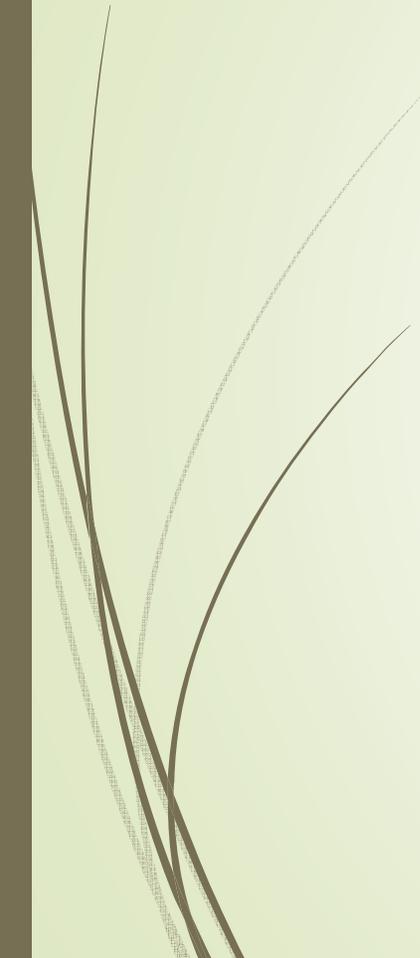


## Treatment of Pain

- No Class I evidence
- Control motor fluctuations
- rTransMagnetic Stimulation (being studied)
- Deep Brain Stimulation of the STN (Subthalamic nucleus)
- Rotigotine (being studied)



## What else are we learning? Motor and Non-motor Subtypes

- Motor subtypes, established already
  - Non-motor subtypes and how they relate to motor subtypes (being studied)
  - Defining non-motor subtypes (being studied)
- 



## Motor Subtypes (defined)

- Tremor Dominant (TD)
- Akinetic/Rigid (AKR)
- Postural Instability Gait Disorder (PIGD)

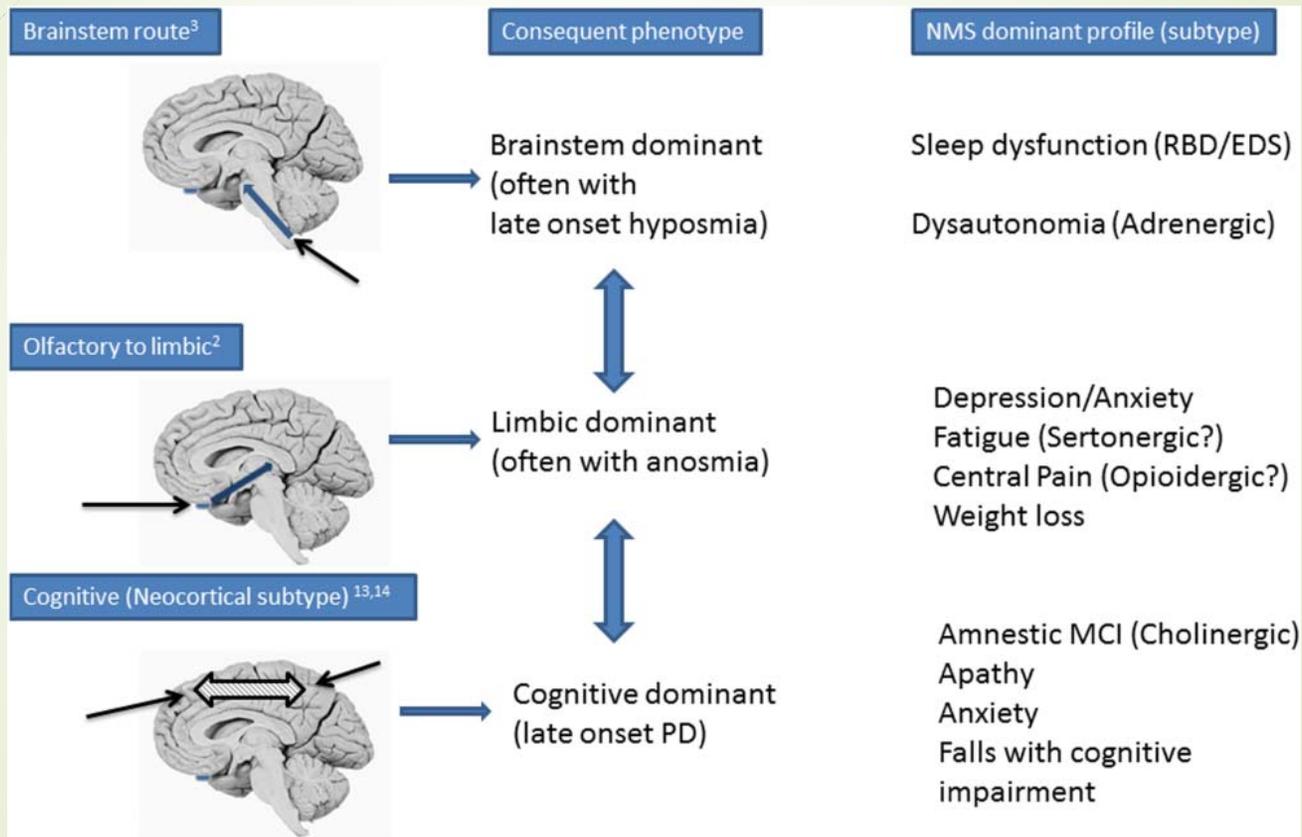


# Non-Motor Subtypes

## ► Biomarker evidence

- Imaging
- Pathological (see next slide)
- Biochemical
  - Serotonin levels lower in spinal fluid patients with Tremor dominant and Akinetic Rigid (AKR) subtype = higher rates of depression??
  - Amyloid deposition higher in PIGD motor subtype = higher rates of earlier cognitive/memory problems??
  - Decrease in norepinephrine uptake in heart uptake in AKR or PIGD = more autonomic problems??
- Overall NON-tremor dominant Parkinson disease may have more broad lewy body deposition

# Non motor subtypes- pathological evidence



Marras, C. and Chaudhuri, K. R. (2016), NMS and PD Subtypes. *Mov Disord.*, 31: 1095-1102. doi: 10.1002/mds.26510

Table 1. Clinical description of NMS-dominant phenotypic variants in well-characterized cohorts of PD (untreated and treated) as described in the literature (adapted from Sauerbier et al, 2015)

Nonmotor domain	Defining features of subtype	Ancillary features
<b>Cognitive</b>	Early and dominant cognitive dysfunction	Older age ( $\geq 72$ years) Non-tremor-dominant motor phenotype associated with falls Poor semantic fluency score ( $< 20$ ) Lower pentagon copying score ( $0 < 1 < 2$ ) Microtubule-associated protein tau (MAPT) H1/H1 genotype possibly a biomarker
<b>Neuropsychiatric</b>	Anxiety/depression	
	A. Anxious-depressed	
	B. Depressed	Postural instability gait disturbance
	C. Anxious	Younger age; Marked motor fluctuations
	Apathetic	Relatively severe motor symptoms (out of proportion to disease duration) Concomitant depression Lower cognitive status Fatigue Good response to dopaminergic drugs
<b>Sleep</b>	REM sleep behavior disorder	Symmetric disease onset Increased periods of freezing Autonomic dysfunction Prone to higher prevalence and severity of orthostatic symptoms Higher rate of depression Visual hallucinations Increased frequency of falls Impairment of color vision
<b>Olfactory</b>	A. Severe loss of olfaction (anosmia)	Dyskinesias; Progressive weight loss
	B. Moderate loss of olfaction	No further weight loss with disease progression
<b>Autonomic</b>	Urinary dysfunction	Early noradrenergic deficit; Postural hypotension



# Why should we care about non-motor subtypes?

- ▶ Non-motor symptoms can predate motor by years!  
So.....
- ▶ Could early type of non-motor symptoms predict prognosis for patient?
- ▶ If we can correlate the relationship of the non-motor symptom to the motor symptoms we may be able to prognosticate!
  - ▶ For example...
    - ▶ Urinary symptoms more significant course? (not yet clear)
    - ▶ REM behavior disorder more associated with older age, male, drops in blood pressure, falls, depression and non-tremor dominant parkinson disease



## In Summary....

- ▶ Parkinson not just a movement disorder
  - ▶ Alpha synuclein/Lewy Bodies in other parts of the body
- ▶ Non-motor symptoms can fluctuate like motor symptoms
- ▶ Dopamine is not the only neurotransmitter affected by Parkinson disease
- ▶ Treatments for non-motor symptoms are being studied now more than ever!
- ▶ Subtypes of Motor and Non-Motor symptoms may give us some help with prognosis
- ▶ Non-motor symptoms affect quality of life more than non-motor symptoms in some patients, which is why it is becoming more of a focus for research

Questions?

