Overview of Parkinson Disease Diagnosis, Cause, Treatment

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Disclosures

- I receive research grant funding from the following commercial entities for research on new Parkinson Disease Therapies
  - Insightec: Makers of equipment for focused ultrasound, now FDA approved to treat tremor dominant PD
  - Neuroderm: Makers of infusible carbidopa/levodopa, not yet approved by the FDA to treat PD
- I will point out any off-label uses

Impact of Parkinson Disease:

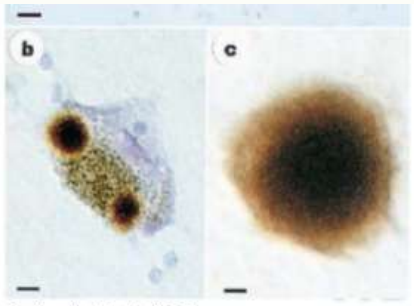
- 1-3% people > 65
- 7-10 million people have PD
- 725,000 US citizens with PD
- 60,000 people diagnosed/year in US
- 4-10% diagnosed < 50 y.o.

Parkinson Disease: Diagnosis What is PD?

- Slowly progressive disease without a cure
- So far there is no imaging or blood test that positively identifies Parkinson disease
- Diagnosis is made clinically in life, and **pathologically** after death
- Blocq and Marinesco (1893)
  - Midbrain TB led to PD symptoms
  - Contradicts Parkinsons who said medulla
- Brussaud implicated SN (1895)

Pathology of PD

- Tretiakoff (1919)
  - Black pigment loss in the **substantia nigra** led to PD
  - Saw **Lewy Bodies**
  - Spillantini (1997)
    - **Synuclein** is a major constituent of Lewy bodies.



Spillantini et al 1997

Role of Dopamine

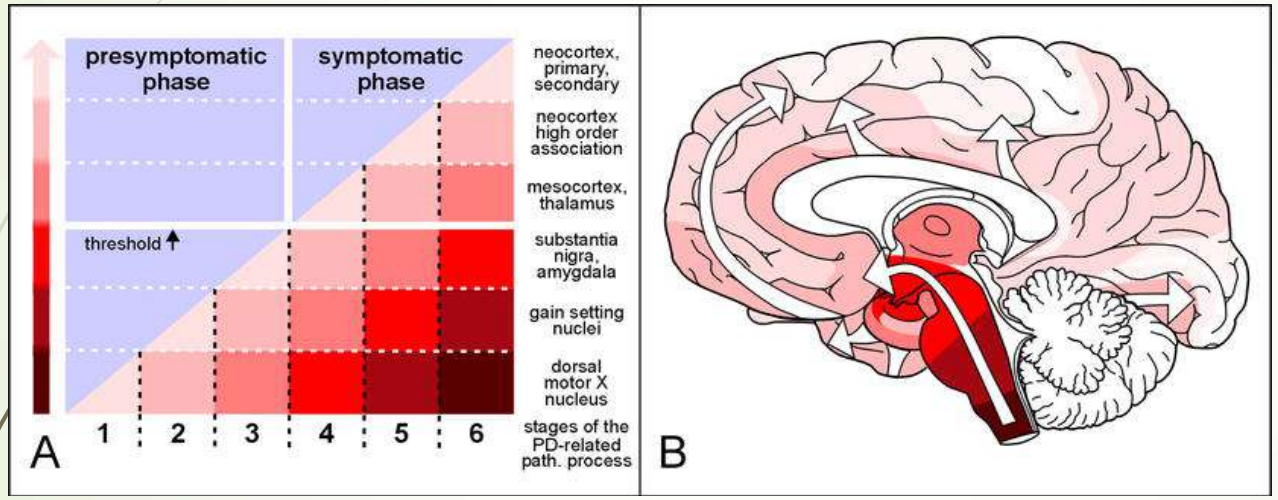
- Arvid Carlsson (1957)
  - Reserpine and Rabbits
  - dopa reduced bunny PD
- Ehringer and Hornkiewicz (1961)
  - Low dopamine in PD
  - Give dopa IV, eased symptoms
- Cotzius (1967)
  - High dose oral dopa worked
- Carbidopa was added and Sinemet was approved in 1972.

"Bed-ridden patients who were unable to sit up, patients who could not stand up when seated, and patients who when standing could not start walking performed all these activities with ease after L-dopa [levodopa]. They walked around with normal associated movements and they could even run and jump. The voiceless, aphonic speech, blurred by pallilalia and unclear articulation, became forceful and clear as in a normal person" (Birkmayer and Hornykiewicz 1961).

PD Pathology

- Loss of pigmented area in the midbrain
- Remaining cells have Lewy bodies
- Lewy bodies have abnormal synuclein
- Loss of cells reduces dopamine

Staging PD Pre-symptomatic and Symptomatic Phases

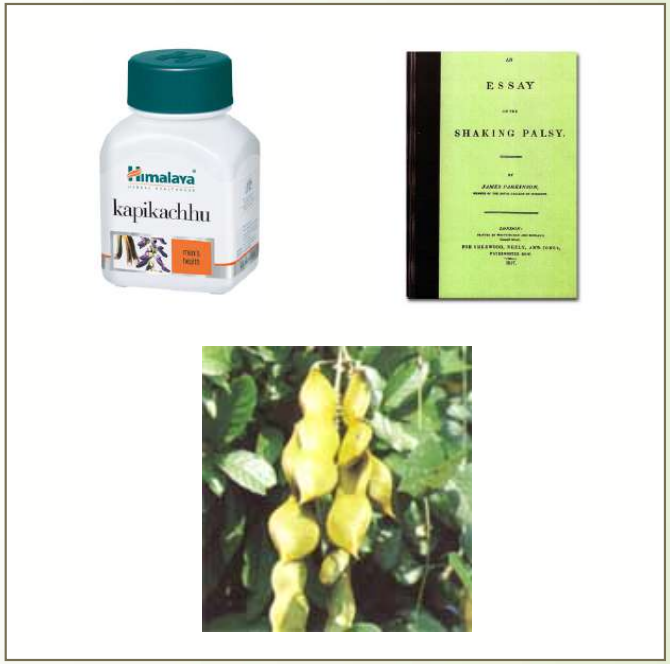


Braak et al Cell Tissue Res. 2004;318:121

PD: Clinical Diagnosis

- Kampavata:
  - Sanskrit ~ 2500/1400 BC.
  - Tremor, drool, stare, stammer, low mood.
  - Mucuna pruriens (Kapikachhu)
- James Parkinson described 6 and examined 2 "patients" in 1817. Paralysis Agitans
- Charcot refined the symptoms and named it late in the 19th century
  - T remor at rest (1 in 5 had no tremor)
  - R igidity
  - A kineisa/ Bradykinesia
  - P ostural instability
  - Added masked face and small writing

Reviewed, Savitt et al. Mol. Neurology 2007



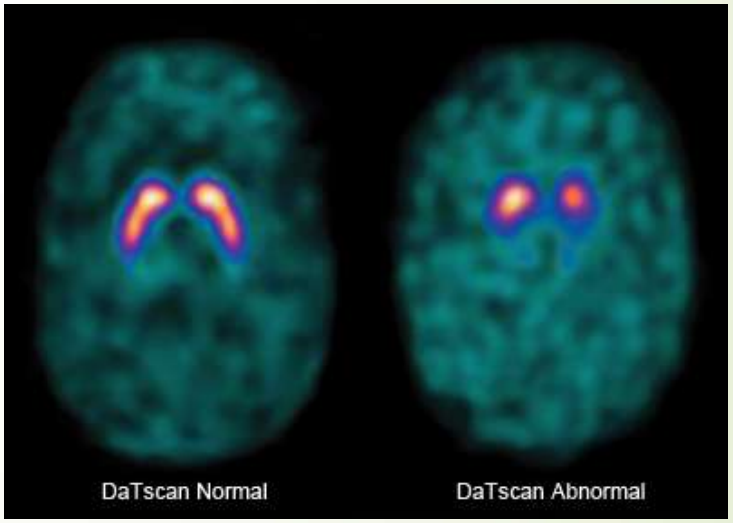
PD: Diagnosis/ Features

- TRAP
- Onset 60 yrs
- Male > Female
- Asymmetric onset
- Anxiety, depression, constipation, hyposmia, masked face, reduced arm swing, soft voice, small writing
- REM Behavioral disorder
- Medication responsive
- Accuracy 76-90%.

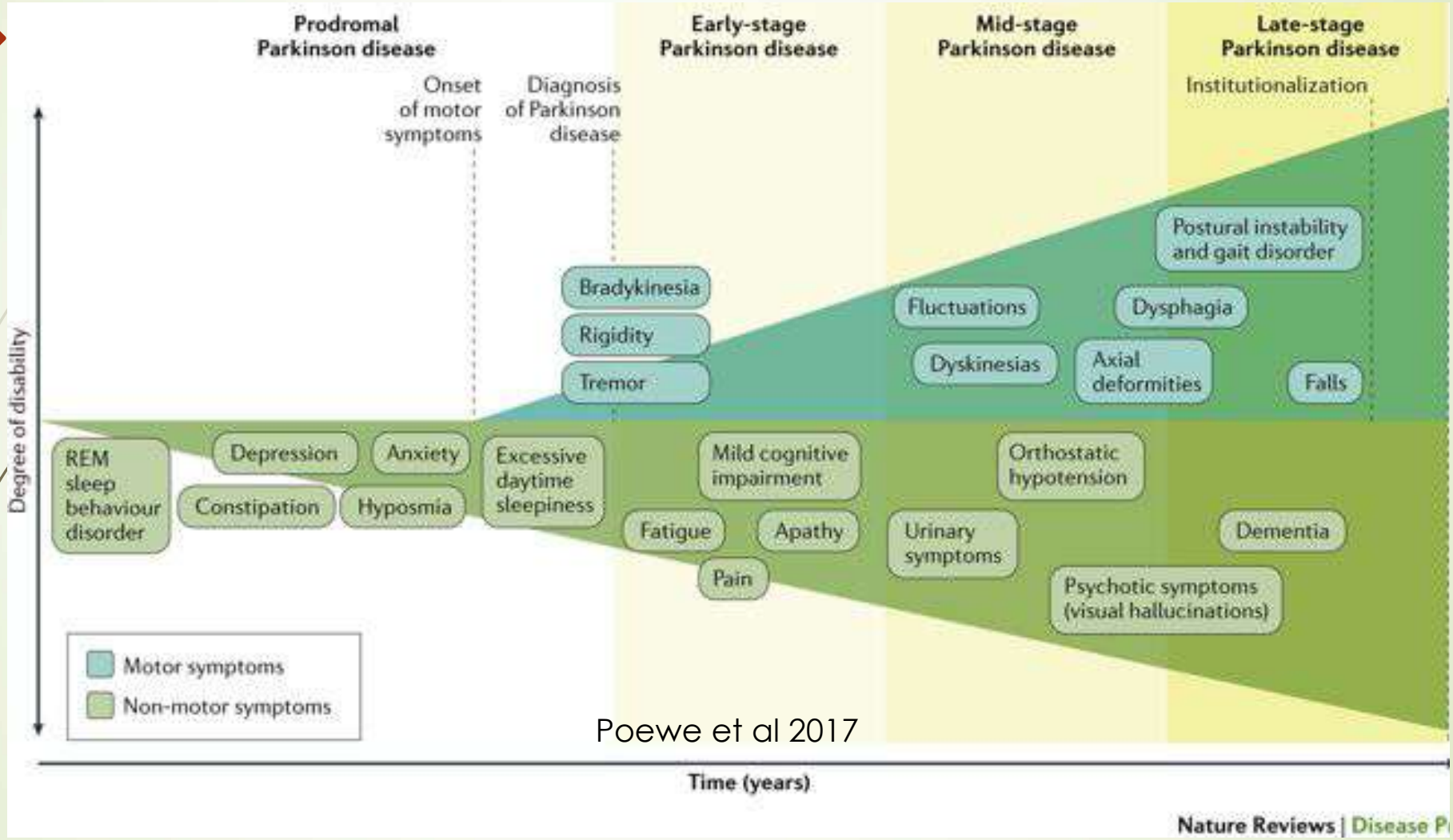
Reviewed in Verbeek J Neurol. 2015, Savitt et al JCI 2006.

DaTscan™ Ioflupane I 123 Injection

- US approved (PD vs ET) in 2011.



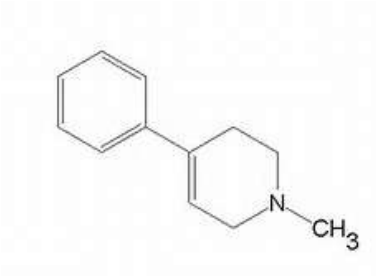
Motor and non motor features of PD



Poewe et al 2017

What Causes PD

- Up through 1980s-90:
  - Environment
    - Post-encephalitic PDism after viral epidemic 1916-1926.
    - Markey and Langston's discovery of MPTP effects
    - 1 Marylander (1976) and 6(1982) Californians



Constantin von Economo

Encephalitis lethargica

Environmental Risks

- **Solvents**
  - **Electricians, dry cleaners, health workers, and machinists** (trichloroethylene > PERC and CCl4 exposure) in study of 198 discordant twins. *Goldman et al Ann Neurol 2012.*
  - Carbon disulfide in French Rayon industry workers linked to Pdism
  - **Painters** exposed to TCE, n-Hexane and other solvents may have greater a PD risk Reis et al 2016
  - Risks: Manganese (welding?) leads l-dopa unresponsive Pdism. *Guilarte, Gonzoler Toxicol. Sci. 2015.*

- Chemicals
  - **Pesticides** can lead to oxidative stress, mitochondrial toxicity, synuclein fibrillization, neuronal death Yan et al 2018. **Well water**
    - Paraquat: Dopamine cell death in culture
    - Rotenone causes PD like pathology in rodents
    - Organochlorine disrupt proteasome function, increase and aggregate synuclein
  - Meta-analysis: pesticide exposure of 5 years increased PD risk by 5% and 10 years by 11%
  - Atrazine, simazine, alachlor and metachlor, permethrin, beta-hexachlorocyclohexane, 2,4-dichlorophenoxyacetic acid, Paraquat (especially in those who genetically have reduced ability to metabolize)
  - Ziram, **maneb** and paraquat exposure triples risk
  - **Agent Orange.**
  - Benomyl (fungicide) exposure increases PD risk and is toxic in fish models of PD and in dopamine cell culture. *Fitzmaurice et al PNAS 2013.*

Environmental Risks

- Infections
  - Nocardia, whooping cough, LPS. H. Pylori infections can model PD in mice. *Slavatore et al abstract, 2011.*
  - PD rates higher after **Hep B and C** infection, *Pakpoor et al 2017*
  - Case control study found OR 7.42 for lifetime **Influenza risk**. *Vlajinac et al Int. J. Neurosci 2013*
  - Pro-inflammatory, reduced butyrate-producing, **fecal microbiome** may increase risk (cause or effect?). *Keshavarzian et al Mov dis 2015.*
  - Severe flu within 10 years of PD onset doubles PD risk. Increased risk after cat and cattle exposure too. *Harris et al. Mov. Dis., 2012.*
- Head Trauma
  - Consensus statement **says little evidence** of a link. (LOC > 5 minutes) with exposure to paraquat triples risk of PD. *Marras et al Arch. Phys. Med Rehabil 2014*
  - **Head trauma in those 55 and older increased PD risk** 44% over those with other trauma over the next 5-7 yrs. Synuclein levels are elevated after head trauma. *Gardner et al Ann. Neurol 2015.*
  - Head trauma with variations in the Synuclein gene increased risk. Goldman et al Ann. Of Neurol. 2012.
  - Mild TBI in Vets increases PD risk by 56% Gardener et al Neurol. 2018
- Protection:
  - **Caffeine: Coffee and tea**, NSAID (Ibuprofen), CCBs, albuterol, tobacco. Role of **GI bacteria**?
  - **Exercise**: 60% reduced risk for 10 months of strenuous exercise/year vs 2 months/year
  - Vitamin D, childhood measles, urate. Peppers, tomatoes, and potatoes contain **nicotine** and may be protective *Nielsen et al, Ann Neurol., 2013*. Yerba mate consumption *Gatto et al, J. neurosci 2015*. Li in tobacco smoke. +/- Statins
  - **Mediterranean diet**

What Causes PD? Genetics?

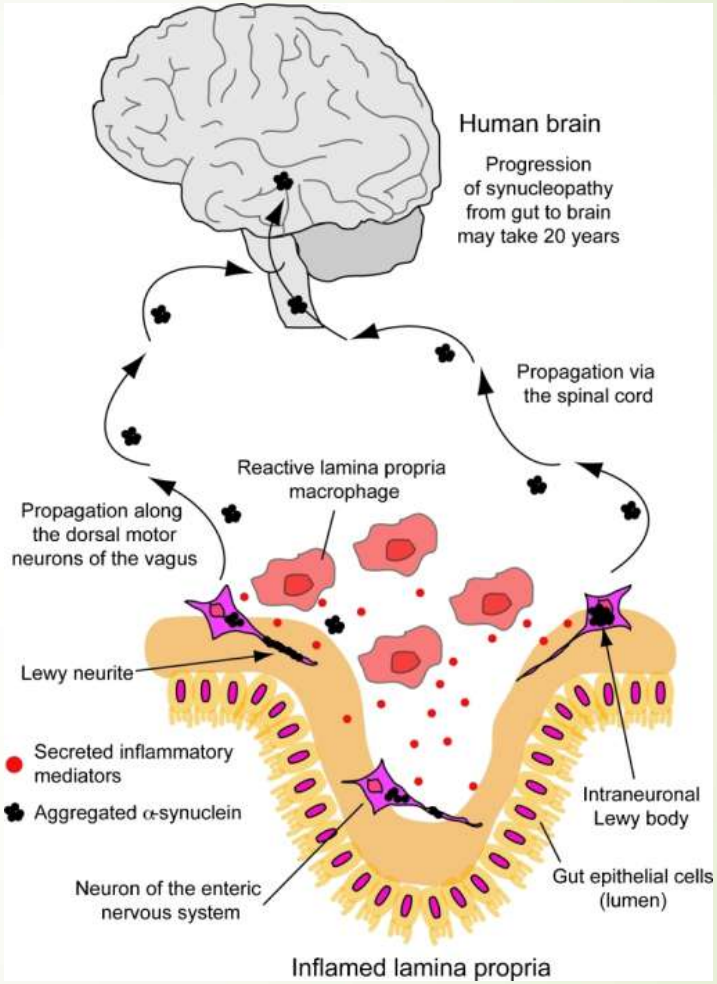
- 5-25% of patients have an affected family member.
- 2-5 % higher risk of PD with a family history.
- Young onset more genetic.
  - Identical twins concordance: <51 yr onset 100%
  - Later onset risk; identical twins = non-identical twins (5-11%)
    Tanner et al. JAMA 1999

Genetics: α-Synuclein

- Syn is a major constituent of Lewy bodies. *Spillantini et al Nature,* ***1997***
- α-synuclein, A53T in an AD, PD family. *Polymeropoulos et al Science,* ***1997.***
- Polymorphisms/duplications / triplications increase PD risk.

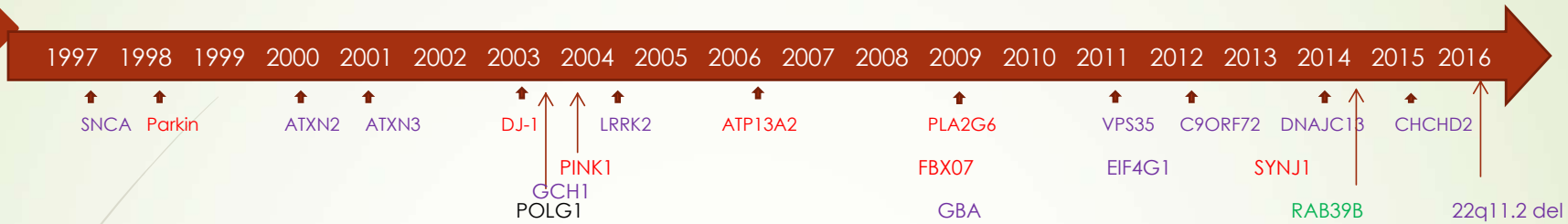
Synuclein Prion Hypothesis

- Synuclein Prions
- Syn monomer > β-sheet aggregate that is toxic
  - Fetal cells transplant
  - Synuclein (preformed fibrils) injection or into Gut of mice.
  - Truncal vagotomy delays PD risk in Danes and Swedes.



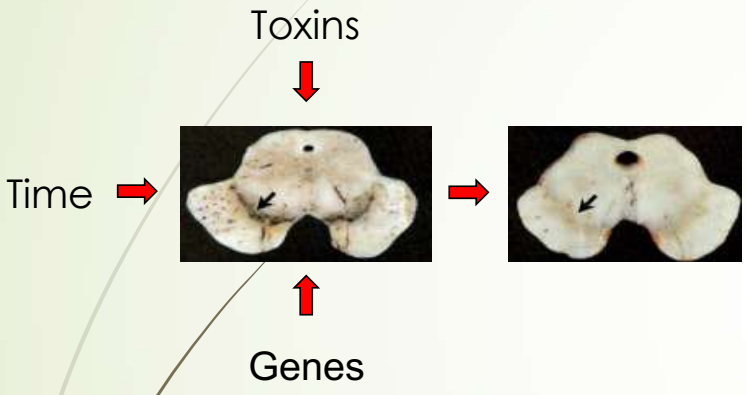
Tome et al. Molecular Neurobiology 47(2), 2012

More Genes

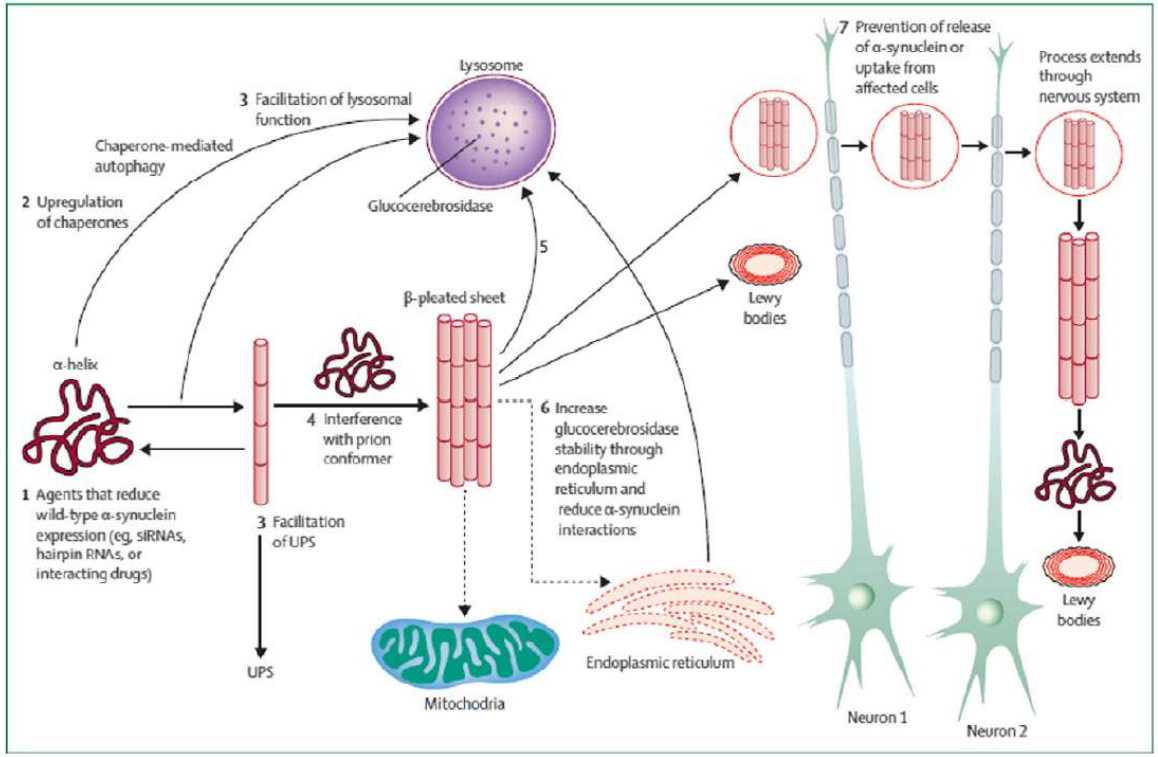


- Common gene changes in 30% of PD. *Mata et al. Mov. Dis. 2012*
- GBA mutation is greatest genetic factor
  - Lysosomal enzyme
  - 2.3-10 % of PD patients
  - sPD patients have reduced GBA activity
  - 30% of 80 yo w/ mutation get PD
- LRRK-2 present in 1-2% of all PD and > 4% of familial cases.
  - May respond to kinase inhibitors
- EOPD more strongly genetic
  - Parkin accounts for 8.6%, PINK-1 3.7 %
    - Involved in mitochondrial maintenance.
    - Mitochondrial biogenesis (Parkin-Paris)
  - DJ-1 0.4% of EOPD.
    - Regulates oxidant defenses in mitochondria and cells
  - Onset under 40, 9.5% genetic, 29% if a person has an affected sibling, 50% if parents are related.

So What Causes PD?



Synuclein
Abnormal transport and signaling
Oxidative stress
Inflammation
-T cells recognizing synuclein
Impaired protein clearance
-Lysosomal enzymes (5 so far) implicated in PD
Mitochondrial damage

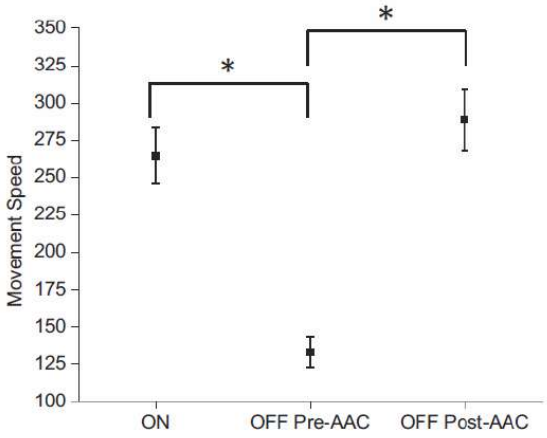


Schapira Mol. Cellul. Neurosci 2015.

Treatment of Parkinson Disease

PD Treatment: Exercise

- Active-Assisted Cycling Improves Tremor and Bradykinesia in Parkinson's Disease. *Ridgel et al Arch Phys Med Rehab. 2012*
- Evidence for weightlifting, Tai-Chi, rowing, dancing too.
- Treadmill 85% max HR > 65% max HR= Controls in PD progression. Schenkman et al 2017 JAMA Neurol.
- Cochrane supports exercise, but cannot tell which is best (RT, ET, OITM each work). Uhrbrand et al J Neurol. Sci 2015; *Cochrane, Tomlinson et al 2014*.



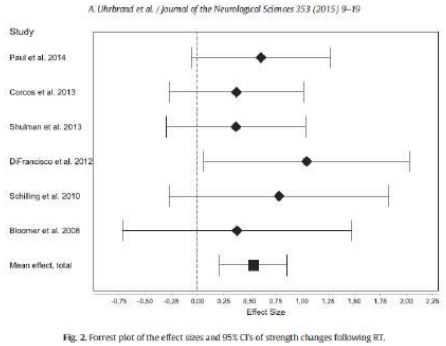
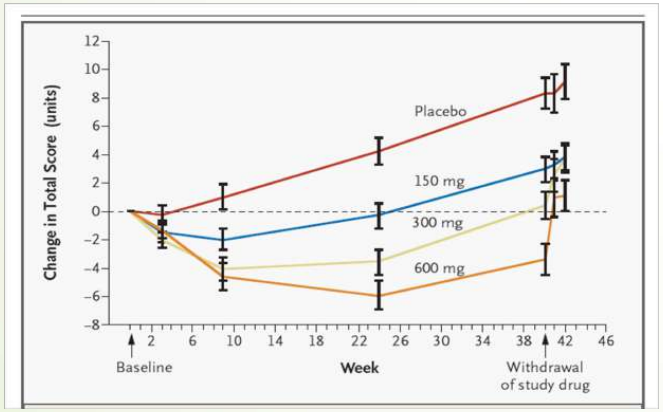


Fig. 2. Forrest plot of the effect sizes and 95% CIs of strength changes following RT.

Carbidopa/Levodopa

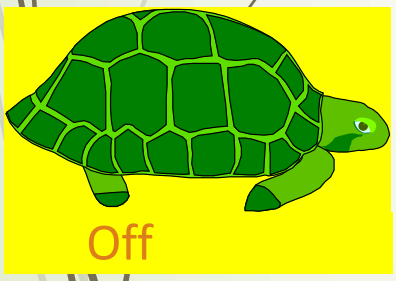
- Utility proved in 1969
- Sinemet launched 1972, CR 1991
- Levodopa is converted to dopamine
- Carbidopa prevents the peripheral inactivation of levodopa.
- Most effective medication



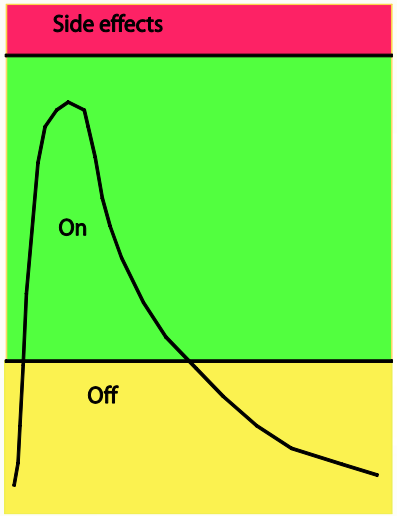
Parkinson Study Group (2004) Levodopa and the progression of Parkinson's disease. N Engl J Med 351(24):2498–2508

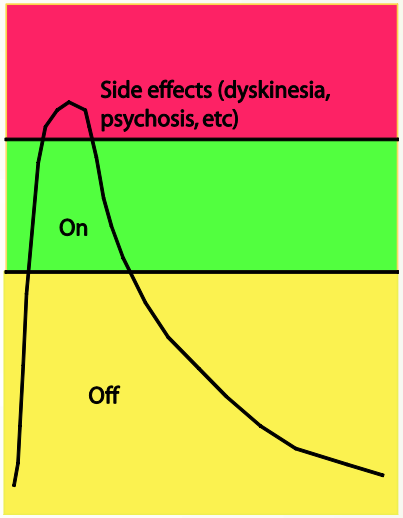
L-dopa is not perfect….

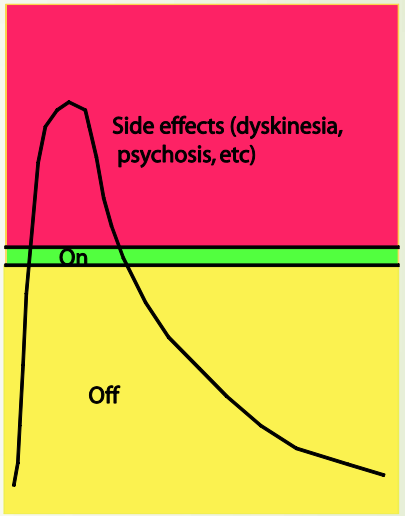
- State of relative mobility
- Medication is "working"
- Reduction in tremor, rigidity and slowness
- Improved mood



- State of relative immobility
- Tremor
- Rigidity and slowness
- Sensory and behavioral phenomena





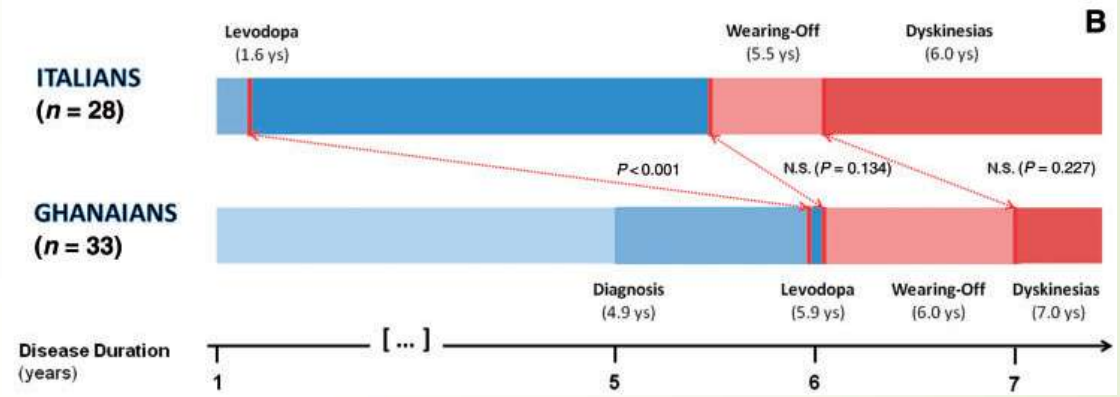


Types of Motor Complications

- Complications
  - Wearing off
  - Delayed on
  - Dose failures
  - Sudden off
  - Hallucinations/ delusions
  - Dyskinesia

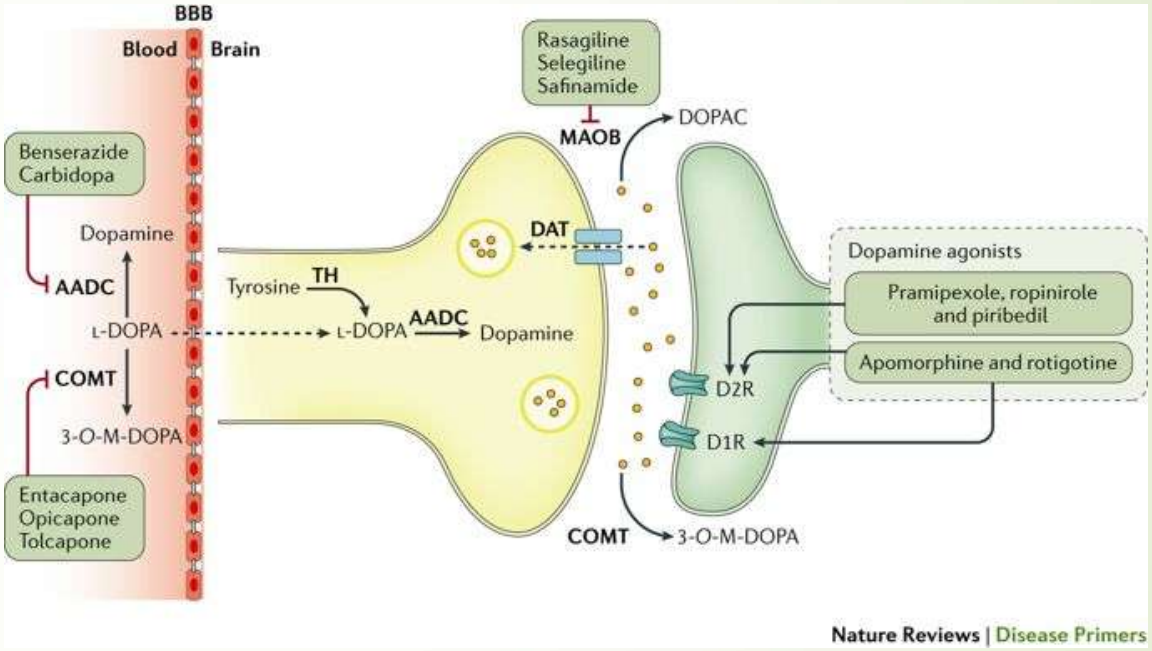
L-dopa Complications

- Risks
  - Longer disease duration
  - Higher l-dopa dose
  - Lower weight (dyskinesia)
  - N. American > European
  - Youth
  - More pulses of drug
  - Genetics
  - Tremor is protective
  - GI bacteria
- Not a risk
  - Time on l-dopa
  - *Cilia et al Brain 2014.*



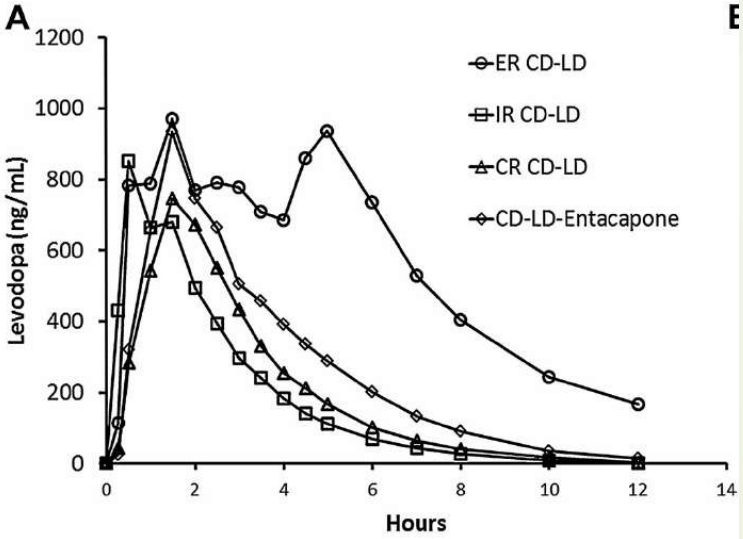
Treat Complications

- Wearing off
  - Move doses closer
  - COMT-I
    - Entacapone
    - Tolcapone
  - MAOb-I
    - Selegiline
    - Rasagiline
    - Safinamide
  - Longer acting l-dopa
  - Dopamine Agonists



Rytary, ER C/L

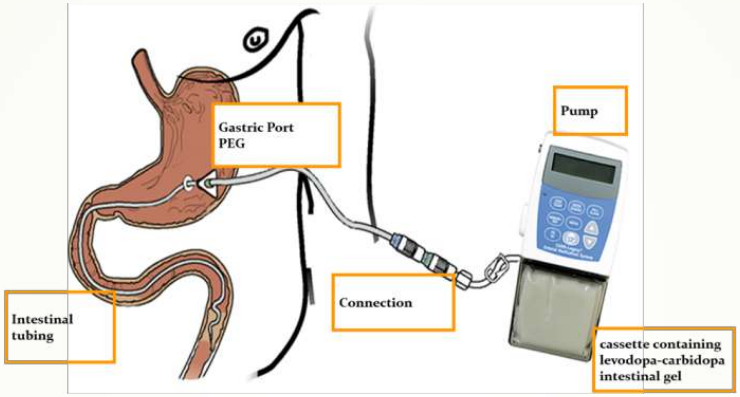
- Approved 1/ 2015
- Reduces off time
- Fewer doses/day
- Reduces dyskinesia

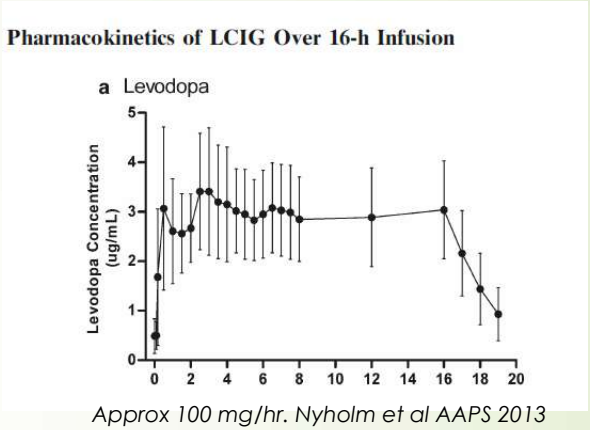


Hauser et al Lancet Neurol 2013, Stocchi et al Parkinson Rel Disord 2014, Waters et al CNS Drugs 2015.

Duopa: C/L Enteral Susp 4.63mg/20 mg /mL

- In Europe since 2004
- Improves off by 4 hrs vs 2hrs from baseline
- Reduces dyskinesia
- Sleep, mood and fatigue improve (GLORIA)
- Concerns about polyneuropathy and device-related complications





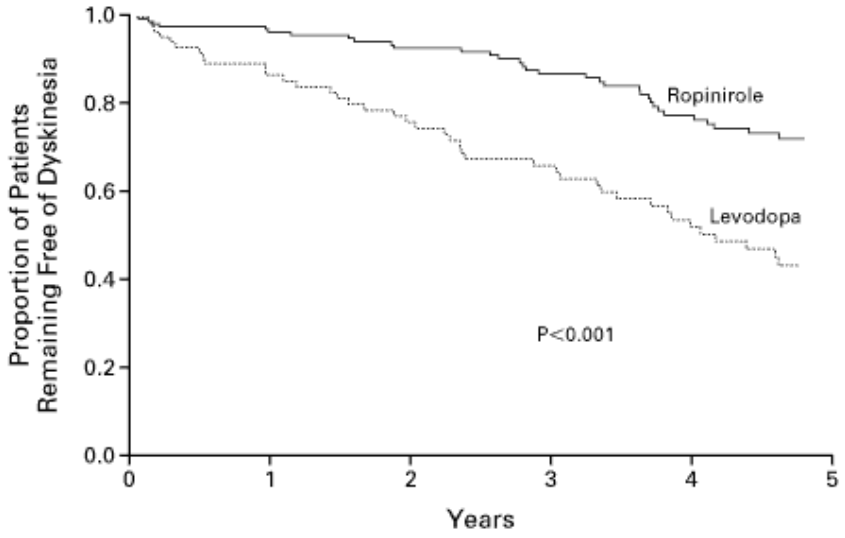
Approx 100 mg/hr. Nyholm et al AAPS 2013

Inhaled Levodopa Rescue

- Acorda-CVT-301 AKA Imbrija
  - Inhaled 42mg x 2 l-dopa
  - Onset 5-15 minutes
  - Risk bronchospasm
  - Cough

Dopamine Agonists

- Choices
  - Pramipexole (Mirapex), ER available
  - Ropinirole (Requip), XL available
  - Apomorphine (Apokyn) injection (rescue)
  - Rotigotine patch (Neupro)
- Side Effects
  - Nausea / vomiting, drowsiness , edema, orthostasis, hallucinations, dyskinesias, constipation
  - Compulsive behaviors
  - DAWS

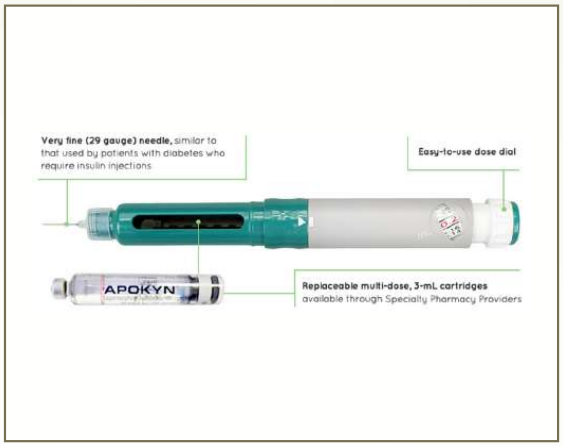


No. at Risk						
Ropinirole	179	143	125	111	101	85
Levodopa	89	73	67	62	56	45
Ropinirole alone	179	126	86	62	45	29

Adapted from Rascol et al 2000 NEJM

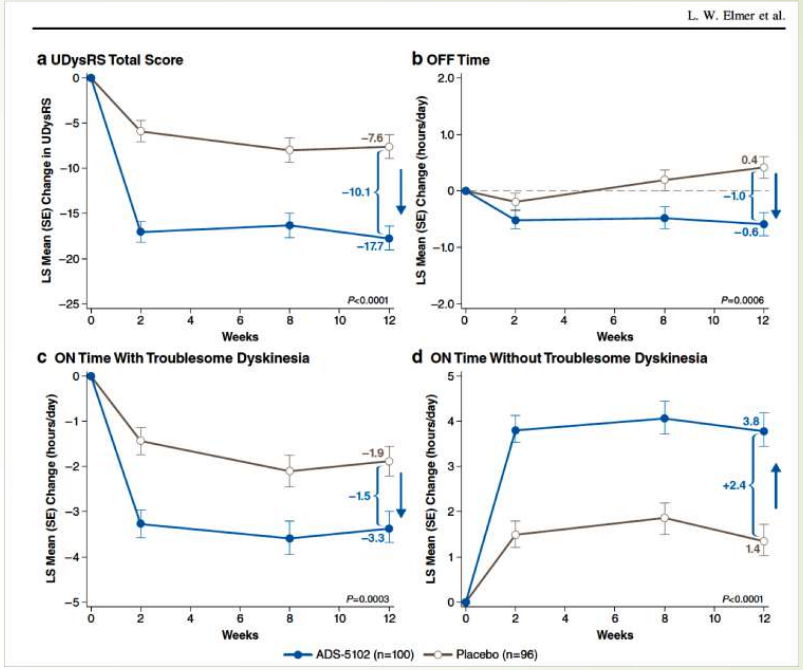
Apomorphine

- Apomorphine
  - Used in US (Apokyn), for rescue of off.
  - Used elsewhere as a continuous infusion (> 30 years)
  - US trials (Infus-On) recruiting
- Cynapsus/Sunovion, APL-130277
  - Thin film apomorphine, five dose strengths
  - 1/30/19: FDA delays approval

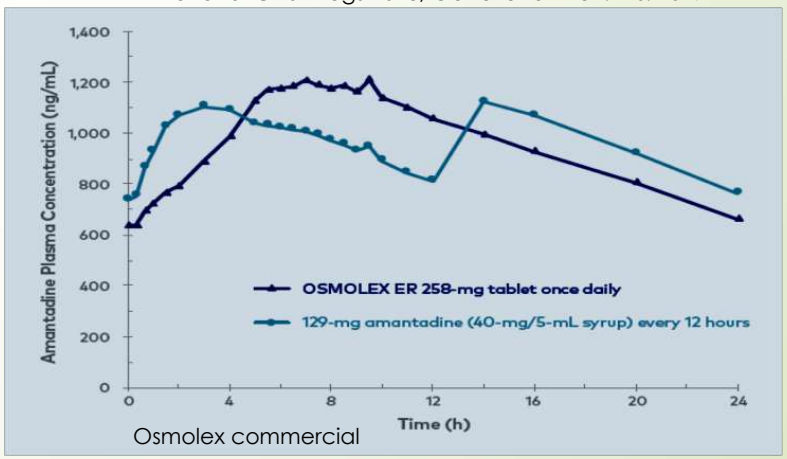


Treating Dyskinesia

- Dyskinesia
  - Reduce PD medication
  - Amantadine
    - Prophylactic for Asian flu approved in 1966
    - Improved PD symptoms found by Schwab in 1969
    - Used for dyskinesia, effectiveness has been controversial
  - ADS-5102, Gocovri (8/2017)
    - 274 mg (340mg amantadine) at bedtime
    - 46 % less dyskinesia, 48% less off time
  - Osmolex (Amantadine ER)
    - Four doses: 129, 193, 258, 322mg
    - Once a day in the morning.



Elmer et al CNS Drugs 2018, Oertel et al Mov. Dis. 2017



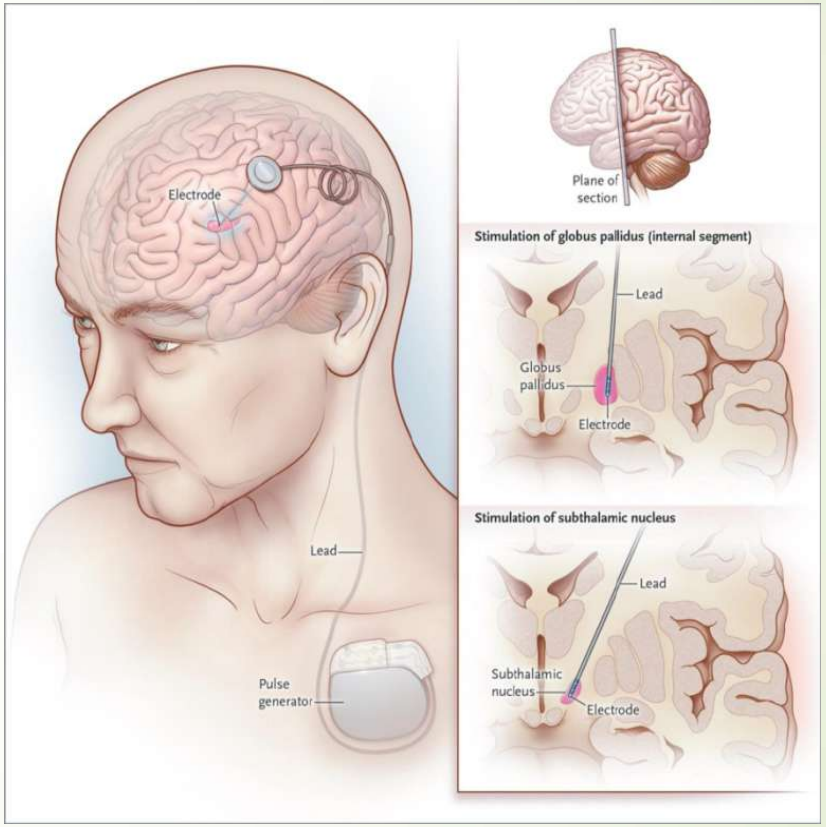
Osmolex commercial

Therapy for Resistant Symptoms

- Tremor
  - Trihexyphenidyl
  - Benztropine
- Memory loss
  - Donepezil
  - Rivastigmine
  - Galantamine
  - Memantine
- Hallucinations/Delusions
  - Pimavanserin
  - Quetiapine
  - Clozapine
- REM behavior disorder
  - Melatonin
  - Clonazepam
- Constipation
  - Fluids, Fiber
  - Miralax
  - Other drugs
- Depression/ Anxiety
  - Anti-depressants
- Urinary Symptoms
  - Pills
  - Botox

Therapies for Resistant Symptoms

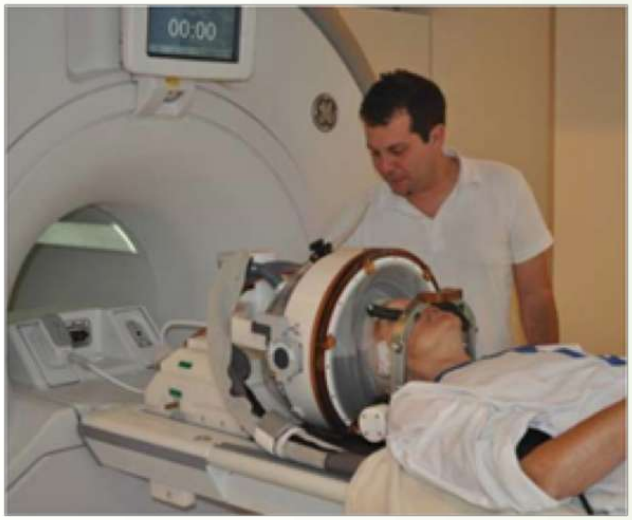
- High frequency, pulsatile, electrical stimulation (Configuration, amplitude, frequency, pulse width).
- Placed into target nucleus (STN, GPi, ViM)
- Improves good on-time
- Reduces refractory tremor
- Using earlier and earlier
- Three companies competing
  - Medtronic
  - Abbott
  - Boston Scientific



Okun et al NEJM 2012

MRI Guided Focused Ultrasound (FUS)

- PD
  - No scalpel
  - > 1000 emitters to head
  - Transient weakness/ tingling
  - Approved for PD tremor
  - Target Pallidum
    - Asymmetric dyskinesia study on-going. Newest study in PD patients starting 2/2018.
    - Targeted pallido-thalamic tract.*Magara etal J. Thera. Ultrs, 2014*
  - Target STN
    - Asymmetric STN in Madrid, 50% UPDRS motor improvement



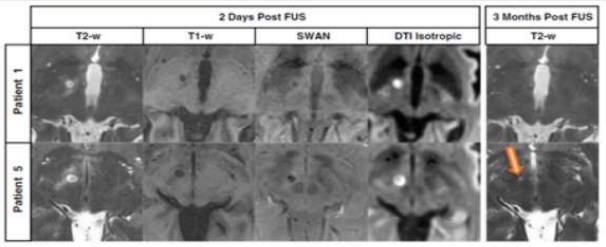


Figure 5 MR imaging differences. Lesion comparison between patient number 1 (group 1) and patient number 5 (group 2) on axial T2-weighted (T2-w), three-dimensional T1-weighted (T1-w), three-dimensional SWAN and Diffusion Tensor Imaging with isotropic post-processing MR series on 2 days and 3 months (only T2-w series) post-operative follow-up. Lesion can be seen on 3 months post-FUS MR imaging only in patient of group 2 (bottom, right). All scans are located 2 mm below the intercommissural plane.

Thanks

Questions?