In the Parkinson's Clinic: What's new and what's next

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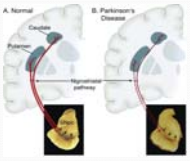
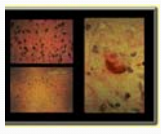
What's new

- ***Diagnosis***
- Cause
- Neuroprotection
- Treatment

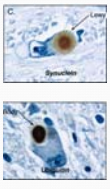
Parkinson Disease: Diagnosis

- There is no objective test for PD in life.
- Diagnosis is made clinically in life; pathologically in death.





Wemove.org



Dauer & Przedborski
Neuron 2003

Parkinson Disease- Diagnosis

- Kampavata:
  - Described in Sanskrit around 2500 BC and 1400.
  - Tremor, drooling, a stare, stammering, and depression.
- Mucuna pruriens (Kapikachhu) treated tremors during the same period and contains l-dopa.

  Singhal et al. *Parkinsonism Rel. Dis.* 2003
- James Parkinson described 6 "patients" in 1817
- Charcot refined the symptoms and named it late in the 19th century.
  - Tremor at rest
  - Rigidity
  - Akineisa/ Bradykinesia
  - Postural instability

  Reviewed, Savitt et al. *Mol. Neurology* 2007

Parkinson Disease- Diagnosis/ Features

- Four cardinal features (TRAP).
- Mean onset 58-62 yrs.
- 10% < age 40.
- Male > Female.
- 5-20% have a family history.
- Asymmetric onset.
- Anxiety, depression, constipation, loss of smell, acting out dreams, etc.

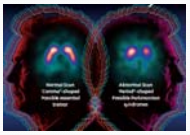
- L-dopa responsiveness
  - PSP: abnormal eye movements, postural instability (accuracy 41-88% PSP)
  - MSA: autonomic dysfunctions, ataxia. (accuracy 50-66%)
  - CBD: asymmetric atrophy, dystonia, FTD-like changes
  - ET: Symmetric, postural, action >rest tremor.
  - Vascular PD: Lower half, older onset.
  - DLBD: early cognitive involvement.
- PD accuracy 76-90%.

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

PD: Diagnostic Aids

DaTscan Ioflupane I 123 Injection See the Difference

- Radio-iodine binds the dopamine transporter
  - Presynaptic pump
- Reduces early in PD (from post. putamen to the caudate)
- Europe since 2000, approved in the US (PD vs ET) in 2011.
- 92-95% sensitive for PD
  - 9% disagreement in reads
  - 82% show correlation with symptom sidedness
  - Correlates better with non-tremor symptoms.
- 80-100% specific PD vs. ET, drug-induced PD, psychogenic PD.
- Impacted by Sertraline, amphetamine, bupropion, methylphenidate, benzatropine, lithium and others)
- Inconsistent result with vascular PDism, DRD
- MSA (more symmetric), PSP (more symmetric), DLB, PD usually abnormal, CBGD can be normal or abnormal.
- LRRK2 and GBA PD patients w/ abnormal, asymmetric scans.



Gayed et al Clin Nucl. Med 2015; 40:390-393,Walker et al BJPsych 2015,.206-145-152, Ba et al ; Parkinsonism Rel Dis. 2015 (21) 2 87-94.

MRI Diagnosis of PD

- 7 T MRI identifies irregular SN border in PD.
  - Likely due to iron accumulation. Kwon et al Annals Neurol. 2012;71:267–277
- DTI imaging found abnormalities in nigrostriatal fibers in PD patients (PPMI) Zhang et al Mov Dis, 2015.
- 3T DTI MRI could differentiate PD, MSA-p, PSP, ET, controls. *Prodoehl et al Mov Dis 2013.*
- fMRI during tasks can see MSA vs PD *Planetta et al Hu. Brain. Map.*
- 3T MRI looking at nigrosome NS1 gave about 92% sensitivity and 91% specificity for PD Schwarz et al Lancet 2014, Noh et al AJNR 2015.

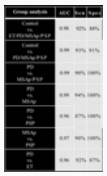
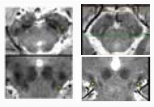


FIG. 2. Findings from logistic regression and receiver operating characteristic (ROC) analyses. Area under the curve (AUC) was the primary outcome variable in the study and is reported for each comparison. Sensitivity (Sen) and specificity (Spec) are also shown.

Prodoehl et al Mov Dis 2013.

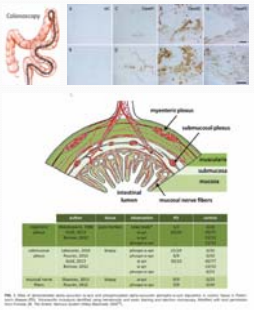


Noh et al AJNR 2015

PD Control

PD Diagnosis: Looking for α-Synuclein in PD

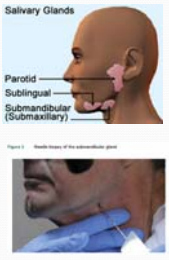
- Synuclein in colon biopsies
  - 3 PD patients, 2-5 years before symptoms.
  - (+) in 9/9 PD patients, not in 23 controls. *Shannon et al Mov Dis 2012*
- F/u article found changes in fecal bacteria that are pro-inflammatory.
  - Lead to altered synuclein
  - Increased colonic permeability *Keshavarzian et al Mov. Dis., 2015.*



- Location of biopsy, timing, age may affect sensitivity. *Visanji et al Mov. Dis. 2015*

Synuclein in other areas.

- Submandibular phospho-synuclein (prot. K) in 9/12 advanced PD. *Adler et al Neurol. 2014; 82 858-864.*
- Synuclein in skin biopsies (11 published studies, variable results)
  - Strongly positive in PD
  - Mildly positive in atypical PD syndromes
  - Skin from neck and back
  - Absent in controls (Mexican study).



Other Diagnostic Aids to come

- Major attempt is underway to find biomarkers (PPMI, Parexel, NINDS-PDBP, Udall).
- Algorithms (83% sen, 90% spec, give 6 people PD for each one properly diagnosed). *Nalls et al/PPMI. Lancet Neurol. 2015, Nalls et al Mov Dis. 2015*
  - olfaction
  - relative with PD
  - age
  - sex
  - **genetic risk analysis** (30 genes)
- CSF tau, p-tau-181, DJ-1, α-synuclein amyloid and b-glucocerebroside in PD. *Hong et al Brain 2010, Montine et al Mov. Disord. 2010, Parnetti et al Nat Rev Neurol 2013.*
- Panel of 4 RNAs is over 80% sensitive and specific for PD. *Grunblatt et al J. Neural Trans 2010.*
  - Similar studies for protein markers.
- Dementia in PD:
  - ApoE e4: increases risk of PDD and Lewy body disease. Arch. Neurol 2012.
  - CSF with high Nfl, heart fatty acid binding protein, and low Abeta 1-42 correlated with PDD. *Backstrom et al JAMA 2015.*

ATP13A2, C9ORF72, FBX07, PLA2G6, POLG1, SCA2, SCA3, SYNJ1, RAB39B
Adapted from Kalia and Lang Lancet 2015

Causes of PD

- Up through the 1980-90s: Environmental factors
  - Post-encephalitic Pdism after viral epidemic around 1915.
  - Markey and Langston's description of PDism in people abusing MPTP.
  - H5N1 bird flu leads to PD-like changes in mouse brain via autoimmune reaction.

Constantin von Economo

Encephalitis lethargica

SO-CALLED FROZEN ADDICTS posed together in 1995, after having received treatment. Nine years earlier all suddenly became immobile, as if they had instantly acquired Parkinson's disease, after taking an impure version of a narcotic. Studies of how an impurity in the drug led to this freezing has generated many insights into the biochemical reactions that could contribute to a more classical presentation of the disease.

Environmental Risks

- Solvent/chemical (TCE, PERC, CCL_4) exposure
  - Electricians, dry cleaners, health workers, and machinists have increased risk of PD (tricholroethylene > PERC and CCl_4 exposure) in study of 198 discordant twins. *Goldman et al Ann Neurol 2012.*
  - Risks: Manganese (welding?) not associated with common PD, leads to l-dopa unresponsive Pdism *Guilarte, Gonzoler Toxicol. Sci. 2015.*
- Pesticides
  - Meta-analysis suggests RR of 1.62 for pesticide exposure. *Van der mark et al Environmental Health Persp. 2012.*
  - Atrazine, simazine, alachlor and metachlor, permethrin, beta-hexachlorocyclohexane, 2,4-dichlorophenoxyacetic acid, Paraquat (especially in those who genetically have reduced ability to metabolize), Maneb, Agent Orange.
  - Benomyl (fungicide) exposure is associated with increased PD risk and is toxic in fish models of PD and in dopamine cell culture. *Fitzmaurice et al PNAS 2013.*
- Head trauma
  - Consensus statement says little evidence of a link. *Marras et al Arch. Phys. Med Rehabil 2014*
  - (LOC > 5 minutes) with exposure to paraquat triples risk of PD (Lee et al., Neurol, 2012).
  - 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)
- Infections:
  - Nocardia, whooping cough, LPS and H. pylori are mentioned frequently. H. Pylori infections can model PD in mice. *Slavatore et al abstract, 2011.*
  - Case control study found OR 7.42 for lifetime Influenza risk. *Vlajinac et al Intnatl. 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.*
- Protection:
  - Coffee and tea, NSAID (Ibuprofen), Tobacco. Role of GI bacteria?
  - Vitamin D, childhood measles, exercise. 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*).

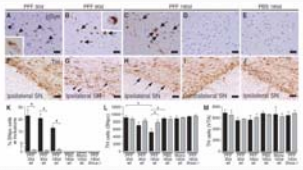
What Causes PD? Is it Genetics?

- 20% of patients have an affected family member.
- Young onset is more likely to have a genetic component.
  - Identical twins concordance: <51 yr onset 100%
  - Later onset risk; identical twins = non-identical twins (5-11%) *Tanner et al. JAMA 1999*

Genetic Causes

- α-synclein, A53T was found in an AD, PD family. *Polymeropoulos et al Science, 1997.*
  - A30P, E46K. *(Kruger et al, Nat Genetic 1998; Zarranz, Ann Neurol 2004)*
  - H50Q, G51D? *(Kiely et al Acta Neuropath 2013, Apple-Crosswell et al Mov Dis 2013)*
- Syn is a major constituent of Lewy bodies. *Spillantini et al Nature, 1997*
- Polymorphisms/ duplications *(Ibanez et al Lancet 2004)*/ triplication *(Singleton et al Sci 2003)* /are associated with increased PD risk.
- Synuclein Prion hypothesis:
  - Synuclein can change from monomer into a beta sheet aggregate.
  - Fetal cells developed synuclein inclusions years after transplant: is taken up by cells. *Desplats et al PNAS 2009, Kordower et al Nat Med. 2008*
  - Synuclein (preformed fibrils) injection leads to PD pathology in mice.
  - Syn oligomers detected by proximity assay show early stage pathogenesis. *Roberts et al Brain 2015.*
  - MSA brain material injected into mice cause synuclein pathology. *Watts et al PNAS 2013.*

Dauer & Przedborski. Neuron 2003



Luk et al Science 2012

More genetics-LRRK2

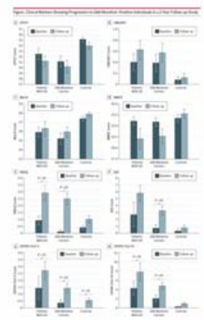
- Mutations in LRRK2 identified in familial PD *(Zimprich et al. Neuron, Paisan-Ruiz et al Neuron 2004).*
  - AD, reduced penetrance.
  - Risk: 28% at 59, 51% at 69 and 74% at 79 years of age. *(Healy et al Lancet Neurol 2008)*
- Common variations in LRRK can increase risk
- Implicated in cancer, IBD.
- May respond to kinase inhibitors, inhibitors may protect against synuclein toxicity.

G2019S in familial and sporadic PD
Lesage et al 2010

Glucocerebrosidase Mutation

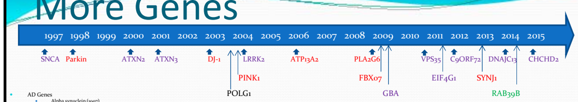
- Greatest PD genetic risk factor is GBA mutation.
  - Encodes lysosomal B-glucocerebrosidase.
  - Gaucher disease when homozygous
  - 2.3-10 % of PD patients have a GBA mutation
  - OR is greater than 5.43 for any mutation
  - 30% of 80 year olds w/ a mutation will have PD.
  - Likely involved in synuclein metabolism
    - GBS activity is reduced in iPD
    - Lower GBA activity leads to higher plasma oligomeric synuclein *Nuzhnyi et al Mov Dis 2015*

- Patients without PD and GBA mutation vs Controls
  - Hyposmia
  - Depression
  - Cognitive impairment
  - REM-Behavioral Disorder
  - Worse PD rating scale score



Mullin/Schapira BMB 2015, Beavan et al JAMA Neruol. 2015, Schapira Mol. Cellul. Neurosci 2015, Sidransky, Lopez Lancet Neurol 2012.

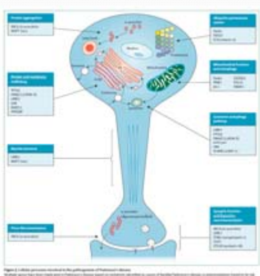
More Genes



- AD Genes
  - Alpha synuclein (1997).
  - LRRK2 (2004).
  - GBA (2009) 30% risk by age 80, prevalence in 2-9%, higher in Ashkenazi
  - VPS35- vesicular trafficking (2011).
  - EIF4G1? (2011)- elongation factor
  - DNAJC13? (2014)-protein trafficking/ chaperone
  - CHCHD2? (2015)- mitochondrial
  - C9ORF 72 (2012) Mixed pathology of hexanucleotide repeat.
- Recessive Genes-early onset.
  - Parkin 15% of early onset familial cases, 4.3 % of early onset sporadic cases. E3 ligase/mitophagy. No Lewy bodies.
  - PINK1 8.4% of early onset familial cases. Kinase involved in mitophagy
  - DJ-1 0.8% of familial and 0.4% sporadic cases. Oxidative stress
  - SYNJ1 (Synaptojanin) Vesicle trafficking
  - X-linked RAB39B Vesicular trafficking

  Recessive Genes-childhood onset
  - PLA2G6 (phospholipase)
  - FBX07 (E3ligase)
  - ATP13A2 Lysosomal (2006)

  - POLG1 AR or AD.
- GWAS (24 loci):
  - GBA (N370S), OR >5. INPP5F, STK39, LRRK2, SIPA1L2, BST1, RAB7L1-NUCKS1, VPS13C, DDRGK1m GPNMB, CCDC62, MIR4697, BCKDK-STX1B
  - SNCA, MAPT, TMRM175-GAK-DGKQ, HLA-DQB1, MCC1, ACMSD-TMEM163, GCH1, RIT2, FAM47E-SCARB2, FGF 20, SRBF1-RAI1. PARK10
- Role of epigenetics/ micro RNA
  - miR-34b/c downregulated in PD Minones-Moyano et al HMG 2011

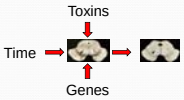


Kalia, Lang Lancet 2015

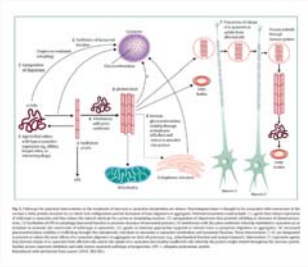
Impact of Genetics

- Common changes in genes increase overall PD risk 30%. *Mata et al. Mov. Dis. 2012* NMD3, SYT4, BST1, MMP16, SNCA, MAPT, GBA (Gaucher disease, OR 3.4), GAK/DGKQ, HLA, ACMSD, STK39, MCCC1/LAMP3, SYT11, CCDC62/HIP1R, STX1B, FGF20, STBD1, GPNMB, RIT 2 and PARK16.
- GBA mutation is greatest genetic factor
  - 2.3-9.4% prevalence
  - 30% of 80 yo with a mutation will have PD
- LRRK-2 accounts for 1-2% of all PD and > 4% of familial cases.
- EOPD more strongly genetic
  - Parkin accounts for 8.6%, PINK-1 3.7 % and DJ-1 0.4% of EOPD.
  - Onset under 40, 9.5% genetic, 29% if a person has an affected sibling, 50% if parents are related.
- Population risk 0.3% with a first degree relative 0.6%.
- 1/3 of Ashkenazi Jews with sporadic PD have either a LRRK2, a GBA mutation or both. *Inzelberg et al JAMA Neruol 2014*

So what causes PD?

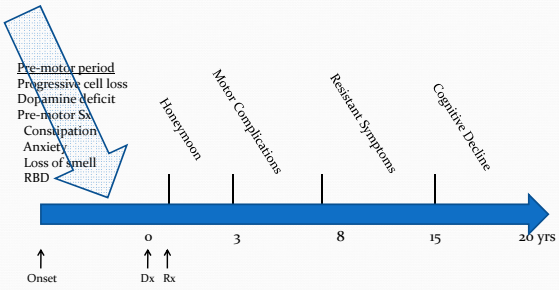


Synuclein
Abnormal transport and signaling
Oxidative stress
Inflammation
Impaired protein clearance
Mitochondrial damage



Schapira Mol. Cellul. Neurosci 2015.

Hope to intervene here with neuroprotection



Why is Neuroprotection Important?

- NPF Quality Improvement Initiative
- After tens years with PD:
  - 44% were minimally disabled
  - 40% had impaired balance
  - 88% could stand without assistance
  - 96% needed l-dopa
  - 46% were on dopamine agonists
  - 37% were on an antidepressant
  - 22% had DBS
  - 93% lived at home

Despite Successes: there remains doubt about MAOb-I

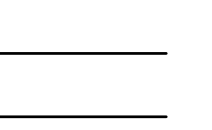
Neuroprotective Trials in PD
MAO-B inhibitors – all successful

YEAR	TRIAL	AGENTS	N	OUTCOME
1993	DATATOP*	selegiline & tocopherol	800	Need for L-dopa
1995	SINDEPAR	selegiline	101	UPDRS change
1996	ROADS	lazabemide	321	Need for L-dopa
2002	BLIND-DATE*	selegiline	368	UPDRS and freezing of gait
2004	TEMPO*	rasagiline	404	Delayed start
2006	Swedish*	selegiline	157	Need for L-dopa and UPDRS
2008	Adagio	rasagiline	>1K	Delayed-start

Adagio Trial: Azilect

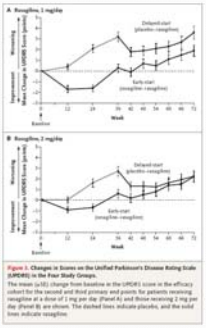
Olanow et al NEJM 2009

Propargyl side chain



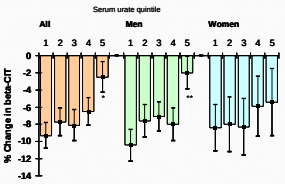
1176 PD patients participated
1 mg/day met pre-specified endpoints
2 mg/day did not

Post-Hoc
-Azilect delayed the initiation of other medications *Rascol et al Lancet Neurol 2011*
-W/ Anti-depressants less worsening of depression, fatigue, sleepiness and cognition *Smith et al JAMA 2015*



Urate

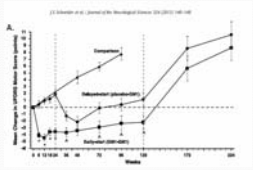
- The higher the Urate, the slower PD progression.
  Ascherio et al Arch. Neurol 2009
- Inosine is safe, tolerable and effective in increasing CSF and serum urate levels.
  Schwarzschild et al JAMA Neurol 2014



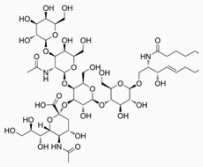
GM1 injections may be protective

- 77 patients randomized
- Symptomatic benefit seen
- Earlier one starts the better
- Imaging supports protection

Schneider et al J. Neurol Sci 2015



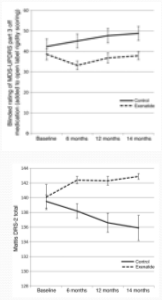
Off scores



Exenatide (Byetta)

Aviles-Olmos et al J Clin. Invest. 2013

- Glucagon-like peptide-1 receptor agonist.
- Neuroprotective?
- **45 patients were randomized and followed for 12 months, then a 2 month washout in an open-label, blinded rater design.**
- SC injection
- UPDRS motor (blinded rater) and Mattis dementia scores improved, even after washout.
- Increased dyskinesias and weight loss in the treatment group.



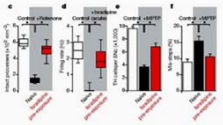
GDNF

Reviewed in Kalia et al Mov Dis 2015, Metman and Slavin Mov Dis 2015.

- 4 GDNF and 2 Neurturin trials have been disappointing so far.
  - Not enough receptors?
  - Down regulation of RET
  - Most recently AAV2-Neurturin in the SN and Putamen failed.
- NIH is conducting AAV2-GDNF convection trial
- PYM50028 (Cogane)
  - oral GDNF/BDNF inducer
  - No change in PD patients at 28 weeks

Neuroprotection- Con't

- Isradipine (CCB) and rejuvenation
  - Several week old mouse nigral neurons use Cav1.3.
  - Younger cells use Na channel (to pace)
  - Young neurons are resistant to MPTP and Rotenone
  - Chan….Surmeier: Nature 2007
  - STEADY-PD (found safe @10mg doses, no clinical effect yet.) STEADY-PDIII ongoing.



C. Dendritic fragmentation
D. Switch to Na pacing
E, F. Protects from chronic MPTP

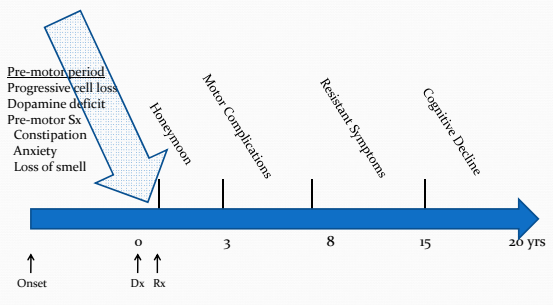
- Nic-PD
  - One year German/ US study in early PD
  - Dose up to 28mg/day
  - Recruiting

- FS-ZONE
  - Piaglitazone in early PD
  - PPAR stimulator, binds to mitochondria
  - Futility met. *NET-PD Lancet Neurol. 2015*

Alpha-Synuclein Therapies

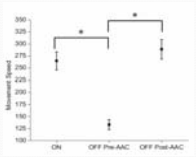
- Target: Disrupt/clear, prevent, or contain pathologic accumulation.
- Immunotherapy
  - AFFiRiS active immunity, using Affitope: short peptide mimicking c-term hSyn w/ carrier. In phase 1 with PD and 2 in MSA. PD01A
  - PRX002: Passive, monoclonal antibody (c-term), blocks cleavage. Lowers serum Syn in controls. Phase 1b with patients ongoing, Prothena/ Roche.
  - BIIB-054 passive , Biogen, Phase 1 control subjects.
  - BioArtic: Humanized monoclonal to syn oligomers. Close, if not already in Humans.
- Small molecule stabilization, small molecule disruption, rev up autophagy pathway.
  - NPT200-11 (Neuropore/ UCB) Oral, stabilizes safe synuclein forms. Humans?
  - Nilotinib: Abl kinase inhibitor to lower Tau and Synuclein.
  - Phenylbutyrate: to remove synuclein from the brain, increases DJ-1. Not yet recruiting.
  - Ceftriaxone: Pre-clinically binds and inhibits Synuclein aggregation.

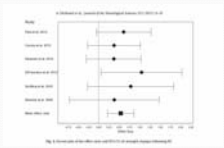
Symptomatic Therapies



Exercise- symptomatic

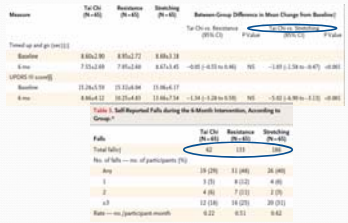
- Active-Assisted Cycling Improves Tremor and Bradykinesia in Parkinson's Disease. *Ridgel et al Arch Phys Med Rehab. 2012*
- Other evidence for weightlifting, rowing, dancing too.
- Cochrane review supports exercise, but cannot tell which is best (RT, ET, OITM each work). Uhrbrand et al J Neurol. Sci 2015; *Cochrane, Tomlinson et al 2014.*





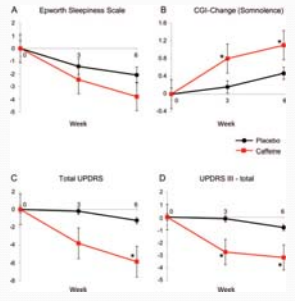
Tai Chi *Li et al NEJM 2012*

- 195 with mild to moderate PD
- Received either Tai Chi, resistance or stretching
- Twice weekly Tai Chi improved balance and reduced falls. Effect lasted for several months.



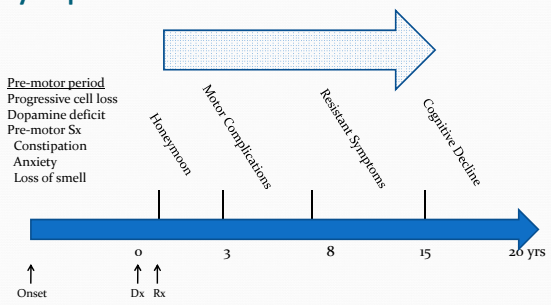
Caffeine

- +/- improvement in wakefulness
- 200mg BID
- Improved motor scores



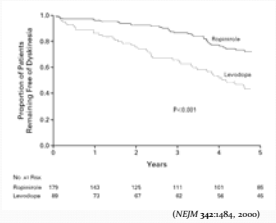
Postuma et al. Neurology 2012;79;651

Symptomatic Medications



Dopamine Agonists

- Options
  - Pramipexole (Mirapex), ER available
  - Ropinirole (Requip) XL available
  - Apomorphine (Apokyn) injection
  - Rotigotine patch (Neupro)
- Side Effects
  - Nausea / vomiting, drowsiness , edema, orthostasis, hallucinations, dyskinesias, constipation
  - Compulsive behaviors
    - 17.1% vs. 6.9% on l-dopa
    - Gambling (5%), Sexual (3.5%), Buying (5.7%), eating (4.3%).
    - *Weintraub et al Arch Neurol 2010*
- ***Better tolerated in younger patients (<70).***



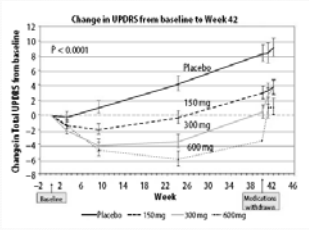
(*NEJM* 342:1484, 2000)

Dopamine agonists (Mirapex, Requip, Neupro in use)

- Apomorphine
  - Used in the US as Apokyn, for rescue of off.
  - Used elsewhere as a continuous infusion, US trials to begin
  - Inhaled apomorphine works within 10 minutes. *Grosset et al Acta Neurol. Scand 2013*
- Cynapsus, APL-130277
  - Thin film apomorphine, five dose strengths
  - Phase 2 trial completed
    - 15/19 patients achieved full "on" from morning "off"
    - 40% turned on <15 minutes, 100% of responders <30 minutes
    - Mean on duration was 50 minutes.
    - *Presented at Mov Disorder 2015, Hauser et al.*

Carbidopa/ levodopa

- Carbidopa/ levodopa
  - Levodopa is converted to dopamine that activates receptor
  - Carbidopa prevents the peripheral decarboxylation of levodopa.
  - Most effective medication
  - Wears off, addition of entacapone (Stalevo) or MAO-b inhibitor helps.
- Side Effects
  - Nausea/vomiting, drowsiness or insomnia, edema of the legs, dizziness, hallucinations, constipation
  - Abnormal movements/ dyskinesias
    - Dose dependent, try amantadine
  - Behavioral disorders



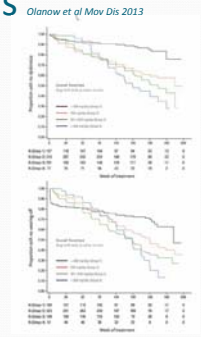
Elldopa

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

Motor Complications

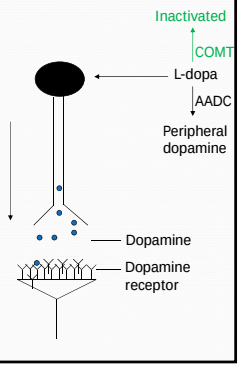
Olanow et al Mov Dis 2013

- Risks
  - Female
  - North American
  - Low weight
  - L-dopa dose
  - Young at onset
  - Worse UPDRS

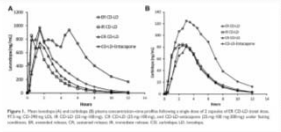


COMT inhibitors

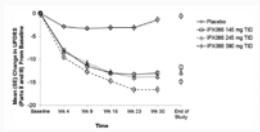
- Prevent the inactivation of l-dopa (Sinemet).
- Smooth out motor fluctuations
- Taken with C/L only
- May worsen l-dopa related side effects, cause GI upset, diarrhea and change urine color.
- Examples
  - Entacapone (Comtan)
  - Tolcapone (Tasmar)
    - Frequent blood tests to monitor for liver failure
  - Stalevo (Sinemet + Comtan)



Extended Release L-dopa: Rytary

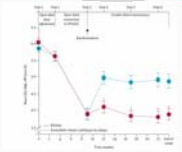


- lasts longer than ordinary l-dopa. *Hsu et al J. Clin. Pharm 2015*
- Can be used TID in *de novo* patients, 70% AUC, 30% Cmax *Pahwa et al Parkism Rel Disord. 2014*

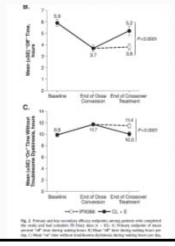


Rytary vs IR

- Rytary given 3.6 times/day reduced off time 1.2 hours versus 5 doses of Sinemet. *Hauser et al Lancet Neurol 2013*
- Rytary reduced off time 1.4 hours more than Stalevo. *Stocchi et al Parkinson Rel Disord 2014.*
- Extension study: 90% of advanced patients dose TID or QID (800-2450mg/day, average 1450). May have reduced dyskinesia. *Waters et al CNS Drugs 2015.*



1621mg Rytary vs 814mg IR

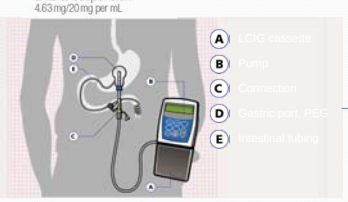


Rytary vs IR

- 75% as bioavailable as IR, need about 2X the total dose.
- Following dose conversion TID, 60% needed more, 16% need less.
- Can dose 3x the individual dose 2/3rds as often. More aggressive than using the tables.

- *Hauser et al Lancet Neurol 2013*

Duopa
carbidopa/levodopa
enteral suspension
4.63 mg/20 mg per mL

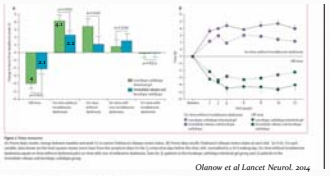


CLES (duodopa) shows improved off time without increasing dyskinesias

Bypasses erratic gastric emptying
Continuous infusion
Can pulse dose
Requires bulky pump, refrigerated storage.

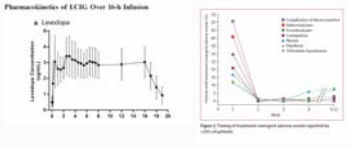
Duopa
carbidopa/levodopa
enteral suspension
4.63 mg/20 mg per mL

- Used in 40 countries.
- Some concern about peripheral neuropathy. B vitamins?
- 12 week double blind double dummy study
- 35 patients received LCIG, 31 oral Sinemet



Olanow et al Lancet Neurol. 2014

- *Catalan et al Mov. Disord, 2013* showed improvement in compulsive-impulsive behaviors
  - 8 of 8 patients with severe CIB improved
  - Punding improved
  - 21% less dyskinesia
  - 27% improved off time.
  - No controls
  - Patient were taken off oral l-dopa and/or agonists too



Approx 100 mg/hr. Nyholm et al AAPS 2013

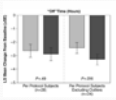
Enhancing l-dopa

- Entacapone increases t1/2 30-60 minutes, AUC by about 30%, about 40 minutes less off time less off time/day *Reviewed , Deane et al Cochrane 2004.*
- Opicapone is qday dosing, not inferior to Comtan. *Reviewed, Rascol et al Mov dis 2015*
- C/L + Ent ODM 101(increased carbidopa) found 0.6 fewer off hours/day.
- Accordion pill (Intec); 12 hours of stomach retention, dosed BID and reduced off time versus QID IR.
- DM-1992, is a bilayer with IR and ER that showed reduction in off time dosed BID +1.3 IR (rescues) vs 4.8 + 0.2 doses of l-dopa. *Metman et al Mov Dis 2015*

Enhancing Levodopa

- Neuroderm, ND0612
  - 360mg infused SubQ/day in 6mL, per pump
  - Can be augmented with oral medications.
  - Phase II, FDA's hold was lifted in 5/2015. Israeli sites and Henry Ford (pending). MJFF funding.
- XP21279
  - Absorbed throughout the GI tract.
  - No difference in off time vs IR (3 doses vs 4-5 doses/day), but less plasma variation on PK studies.



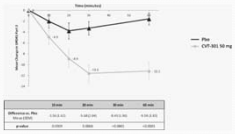


LeWitt et al Mov. Dis. 2014

Levodopa

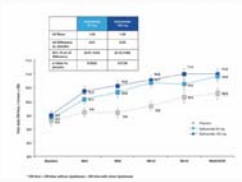
- Melevodopa
  - Metylester (liquid) allows more rapid/regular absorption. *Reviewed, Rascol et al Mov dis 2015*
- Synagile/Dopafuse.
  - Device pumps C/L into the mouth continuously.
  - Phase 2a found reduced off time, company's website.
- Sensidose/Flexilev
  - Frequent microtablet dosing

- Acorda-CVT 301 program
  - Self-administered inhaled levodopa powder for rescue.
  - Peaks at 15 minutes
  - Onset 10 minutes, reducing off time 30%, no increased dyskinesia, used BID on average. Lasts about 100 minutes
  - Phase 3 trial on-going



Treating Fluctuations

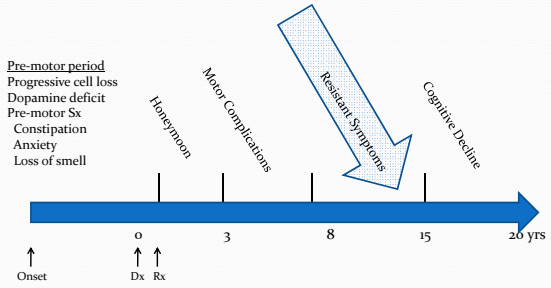
- Safinimide (Xadago)
  - Reversible MAOb inhibitor
  - Na channel blocker, glutamate modulator
  - Improves off time without increased dyskinesia
  - F/U study found improved dyskinesia, depression, QoL at 24 months *Borgohain et al Mov Dis 2015*
  - Licensed in the EU for add-on therapy in PD.
  - Under review in the US



- ADS-5102/ ADAMAS
  - Long acting amantadine.
  - Peaks at 12 hours
  - 340mg qhs reduced dyskinesias by 27%, increased on time, *Pahwa et al Mov Dis 2015.*
- Eltoprazine
  - 5-HT1a and B
  - Anti-dyskinetic in preliminary trials. *Svenningsson et al Brain 2015.*
- Tozadenant/Biotie
  - A2A antagonist, (reduces thalamic activity).
  - Reduced off time 1.2 hr
  - Dyskinesia, nausea, dizziness *Hauser et al Lancet Neurol. 2014*
  - Phase III on-going.
- Istradefylline
  - Adenosine A2A antagonist
  - Reduced off time by about .75 hour/day. *Mizuno et al Mov Dis. 2013*
  - Failed last attempt at FDA approval.
  - In Japan since 2013.

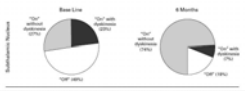
Borgohain et al Mov Dis 2014

Symptomatic Therapies

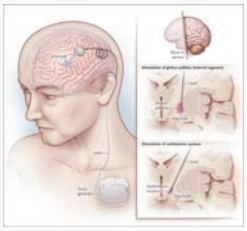


Deep Brain Stimulation (DBS)

- High frequency, pulsatile, electrical stimulation (Configuration, amplitude, frequency, pulse width).
- Placed into target nucleus (STN, GPi, ViM)
- Improves good on-time
- Reduces refractory tremor



NEJM 345:956, 2001

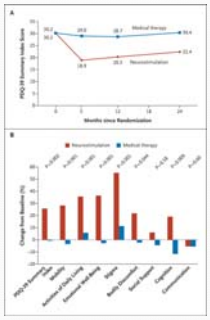


Okun et al NEJM 2012

Not Too Early for DBS

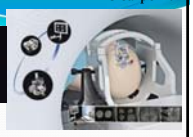
Schuepbach et al *N Engl J Med 2013;368:610-22.*

- 2013 NEJM article
  - 251 patients
  - Average disease of 7.5 yrs
  - Average age 52, 5 years of l-dopa.
  - Early motor complications in patients
  - QOL improved in STN DBS
    - Motor scores
    - ADL
    - Motor complication
    - On time
- Study on early stage PD planned, pilot study found reduced drug dosages needed (about 2yrs w/o motor complications). Reviewed in, *Metman and Slavin Mov Dis 2015, Charles et al PD Rel Dis 2014.*



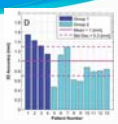
DBS-techniques

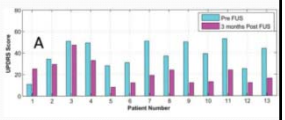
Clearpoint

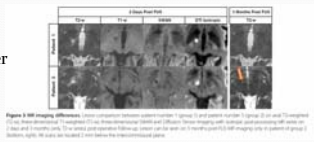


- GPi vs STN
  - Recent study prefers STN for UPDRS improvement on secondary outcomes.
    - Improved off scores
    - Reduced drug doses
    - Reduced voltages and PW. *Odekerken et al Lancet Neurol 2013*
  - Older studies reached no consensus except GPI may be better for cognition.
  - Tremor dominant patient's gait responds better to GPi, PIGD respond less well to DBS, otherwise targets are similar. *Katz et al Ann Neuol. 2015*
- PPN
  - May be a future target for axial symptoms, FOG. Low frequency unilateral PPTG may be effective. *Mazzone et al Gait Posture 2014*
  - Results have been variable.
- Intra-operative CT
  - Allows for guidance and MER
  - May have improved accurracy
  - Could try without MER under general anesthesias
- Intra-operative MRI Guided DBS
  - Patient may remain asleep
    - Preferable to most
    - No microelectrode recording
    - No intra-op exam.
  - Burr hole mounded device, no frame.
  - Usually requires one pass (28/34 times).
  - Accounts better for brain shift after burr hole placement.
  - Latest studies using next generation system had all one pass, targeting error 0.6mm *(Ostrem unpublished).*
  - Specialty groups using it have been successful. *Ostrem Clin, Neurol, Neurosurg 2013, Silbay et al Clin Neurol Neurosurg 2014.*

Lesioning

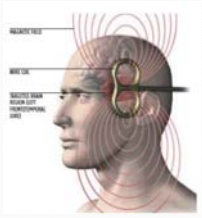






- FUS with MRI guidance could lead to focused lesioning.
  - Seen success in ET thalamotomies.
  - One study in PD
    - Targeted unilateral pallido-thalamic tract.
    - Patients 1-4 received fewer session than 5-13. *Magara et al J. Thera. Ultra. 2014*

Repetitive transcranial magnetic stimulation.



- rTMS studies ongoing for PD.
  - High frequency over M1
  - Low frequency over the frontal area
- Literature review *Zanjani et al Mov Dis 2015, Chou et al JAMA Neurol. 2015*
  - No placebo effect seen?
  - Within one day, motor scores improved 3.8 points on UPDRS III
  - Longer term data is hard to interpret.
  - Thought to increase dopamine levels after M1 stimulation, plasticity?
  - More studies are needed.

Non motor symptoms?

- Psychiatric
  - Depression
  - Anxiety 56%
  - Apathy
  - Behavior
  - Impulse control problems
  - Panic attacks
  - Hallucinations, delusions, illusions
- Cognitive function
  - Concentration (31%)
  - Memory
  - Executive dysfunction
  - Delirium, dementia
- Sleep
  - Insomnia 37%
  - REM behavioral disorder
  - Sleepy during the day
  - Restless legs, PLMS
  - Non-REM parasomnias (wandering)
- GI
  - Drooling 31%*
  - Nausea
  - Constipation
  - Abnormal swallow
  - Bloating
- Fatigue 58%
- Urinary 35%
  - Incontinence
  - Urgency
  - Going at night
- Cardiovascular/ dizziness
- Sensory
  - Abnormal sense of smell
  - Abnormal sense of taste
  - Vision trouble (blurred, double, reduced contrast)
  - Pain (leg 38%)
- Other
  - Change in weight
  - Sexual dysfunction
  - Falls*
  - Skin changes
  - Abnormal temperature regulation
  - Respiratory(cough/SOB)*

Droxidopa (Northera)

- FDA approval 2/2014, NE conjurer.
- Used in Japan for OH and freezing to 300mg TID since 1989.
- Action may be blocked by carbidopa/ enhanced by COMT-I
- Improved falls by 68%
- May have other central NE effects (fatigue, apathy, ADD)

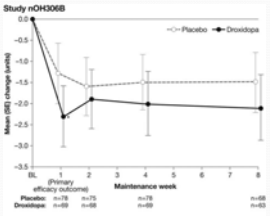
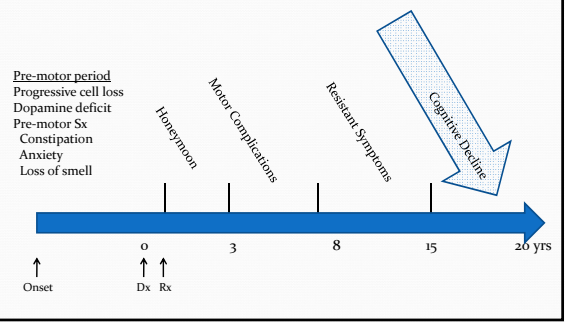


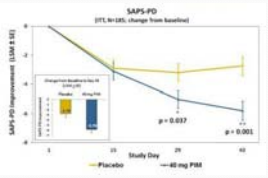
FIG. 2. OHSA item 1 changes from baseline in study nOH306B and study nOH306 overall (observed cases). *P < 0.05 versus placebo, ANCOVA; **P < 0.01 versus placebo, ANCOVA. BL, baseline; SE, standard error.
Hauser et al al Mov Dis 2014

Symptomatic Therapies

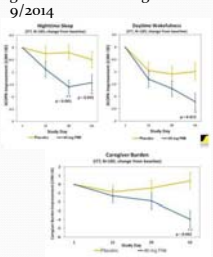


Pimavanserin (Nuplazid)

- Phase III trial of Pimavanserin improved PD psychosis
- 5-HT2A inverse agonist
- 40mg once/ day



- Motor function not worsened
- Global impression was improved.
  Cummings et al, Lancet 2014
- ~~Another study planned~~, FDA granted breakthrough status 9/2014



RESEARCH PAPER

Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis

Gennaro Pagano,[1,2] Giuseppe Rengo,[3] Giuseppe Pasqualetti,[4] Grazia Daniela Femminella,[4] Fabio Monzani,[4] Nicola Ferrara,[2,3] Michele Tagliati[5]

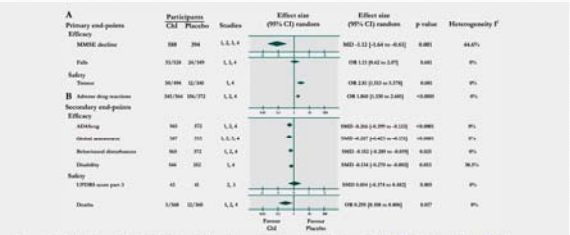


Figure 3 Pooled analyses (SMD and odds risk ratio) for efficacy and safety end points. 1=Emre *et al* 2004[21]; 2=Ravina *et al* 2005[24]; 3=Chung *et al*[22]; 4=Dubois *et al* 2010.[23] MMSE, Mini-Mental State Examination; ADAScog, Alzheimer Disease Assessment Scale-cognitive subscale; UPDRS, Unified Parkinson Disease Rating Scale; ChI, cholinesterase inhibitor; MD, mean difference; SMD, standardised MD.

J Neurol Neurosurg Psychiatry 2014;

Original Investigation

Combined Rasagiline and Antidepressant Use in Parkinson Disease in the ADAGIO Study

Effects on Nonmotor Symptoms and Tolerability

Kara M. Smith, MD; Eli Eyal, MSc; Daniel Weintraub, MD; for the ADAGIO Investigators

Table 3. Changes in Nonmotor Symptoms Over Time in the Pooled Rasagiline and Placebo Groups

	Estimated Change at Week 36[a]				
	Mean (SE)				
Variable[b]	Pooled Rasagiline	Placebo	Rasagiline–Placebo Difference	95% CI	*P* Value
Depression	0.57 (0.07)	0.76 (0.07)	−0.19 (0.10)	−0.38 to −0.002	.048
Anxiety	0.76 (0.07)	0.87 (0.07)	−0.12 (0.10)	−0.31 to 0.08	.23
Apathy	0.48 (0.07)	0.65 (0.06)	−0.17 (0.09)	−0.35 to 0.02	.07
Cognition	0.31 (0.04)	0.50 (0.03)	−0.20 (0.05)	−0.30 to −0.10	<.001
Daytime sleepiness	0.43 (0.07)	0.68 (0.06)	−0.24 (0.09)	−0.42 to −0.07	.006
PFS score	2.41 (0.06)	2.83 (0.06)	−0.42 (0.09)	−0.59 to −0.24	<.001
Sleep	0.75 (0.07)	0.65 (0.06)	0.10 (0.09)	−0.09 to 0.28	.30


Thanks.
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