~~Six~~ myths about Parkinson's disease (and why they are wrong)

ERIG Meeting

27th April 2019

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The University of Edinburgh
Edinburgh Neuroscience

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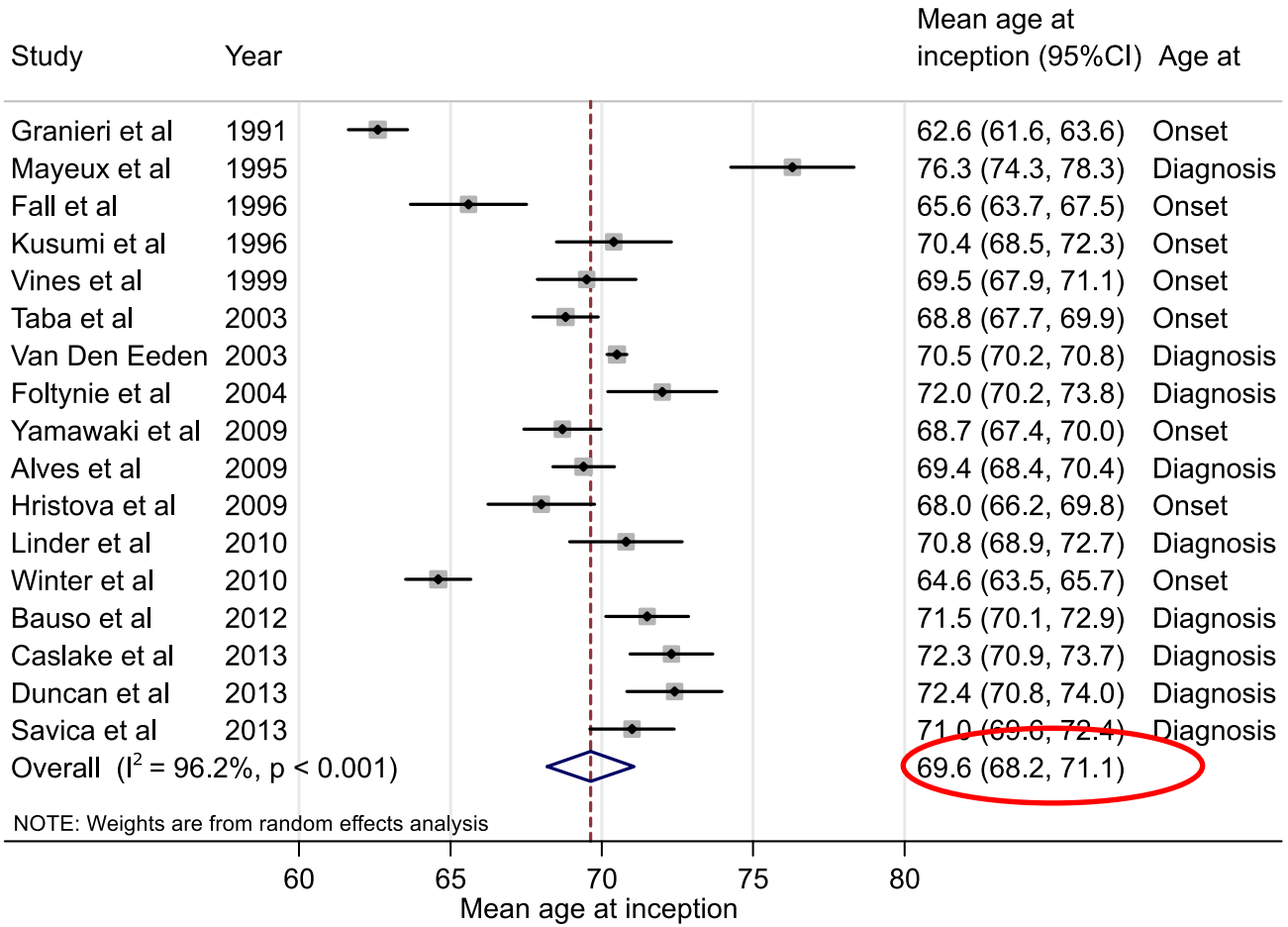
Myth 1: “PD only affects older people”



MacLeod et al, Park Relat Disord 2018

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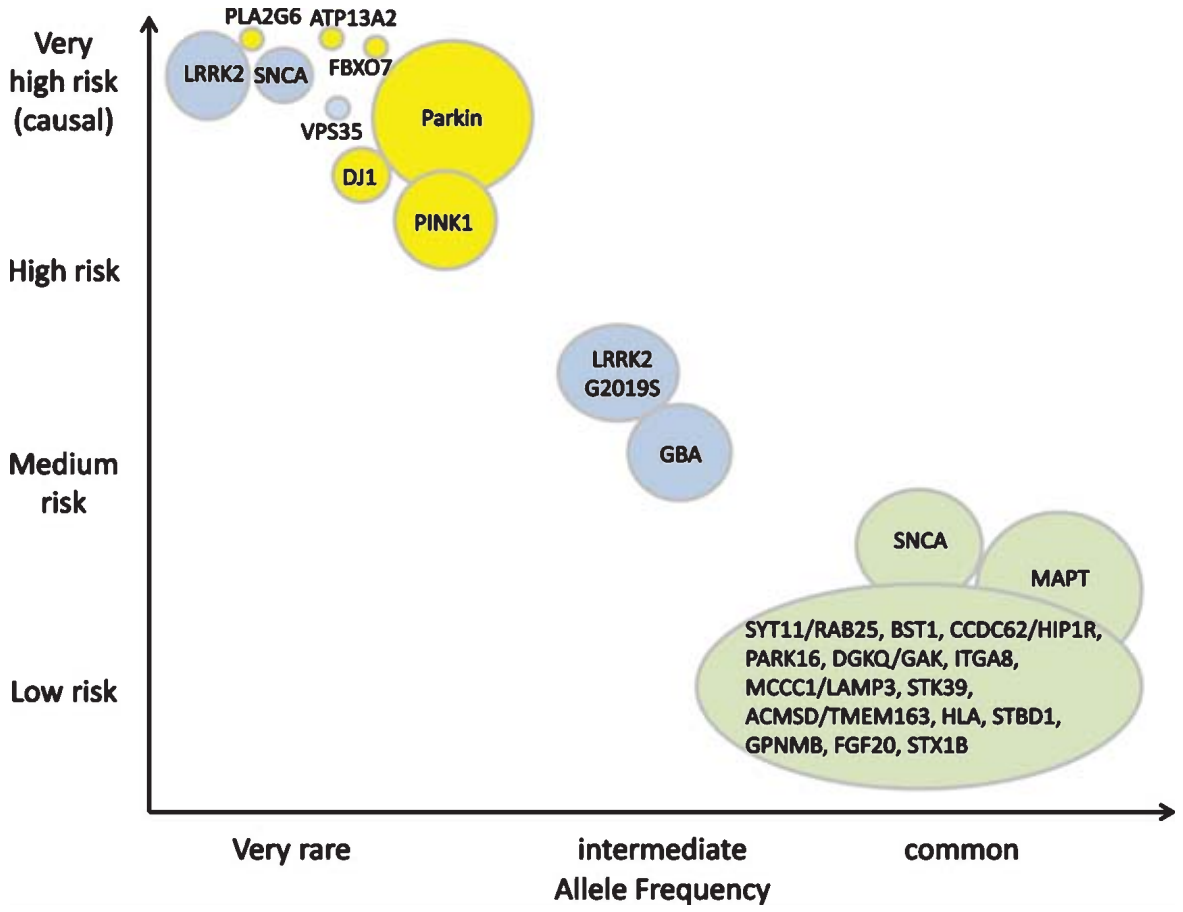
Genetics of PD



YOPD look different clinically

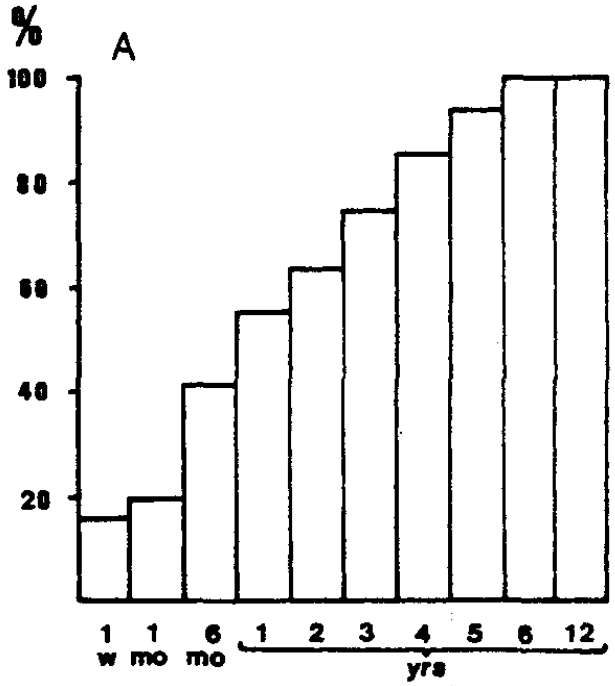
Patient with homozygous Parkin mutations

24 patients with homozygous Parkin mutations

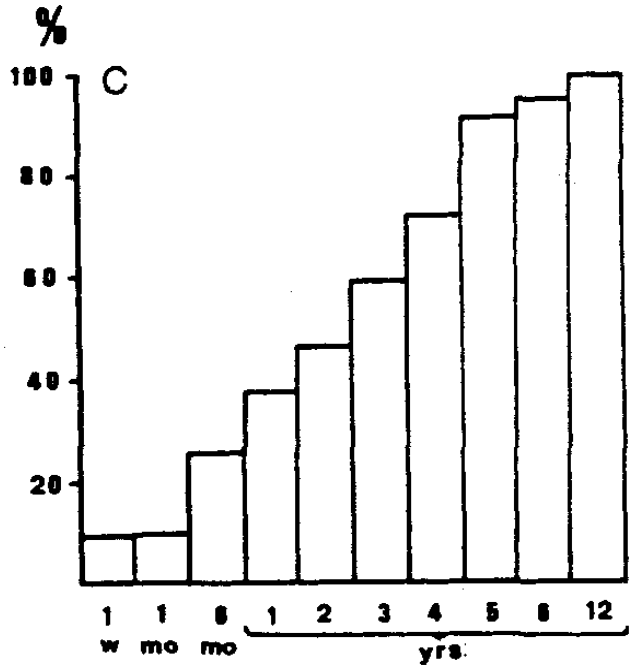
- Mean age of onset = 24 years
- 41% dystonia and 23% poor balance at onset
- 92% with tremor (frequently lower limbs)
- Prominent freezing, falls, autonomic and behavioural disturbances

Khan et al, Brain 2003

Motor complications



Dyskinesias



Motor fluctuations

Quinn el al, MDJ 1993

YOPD support groups

Edinburgh Young Parkinson's Support Group

Aim

Our aim is to provide support to people of "working age" who have PD, in a very informal, relaxed meeting in a private function room kindly given to us by The Steading, 118-120 Biggar Road Edinburgh, EH10 7DU on the **first Thursday** of every month at 6.30 / 7.00 pm (any changes will be notified by email).

Spotlight YOPD

UK-based charity - with a global reach - for YOPD.

Mutation-specific therapies

The Cure Parkinson's Trust

VAN ANDEL INSTITUTE

DENALI

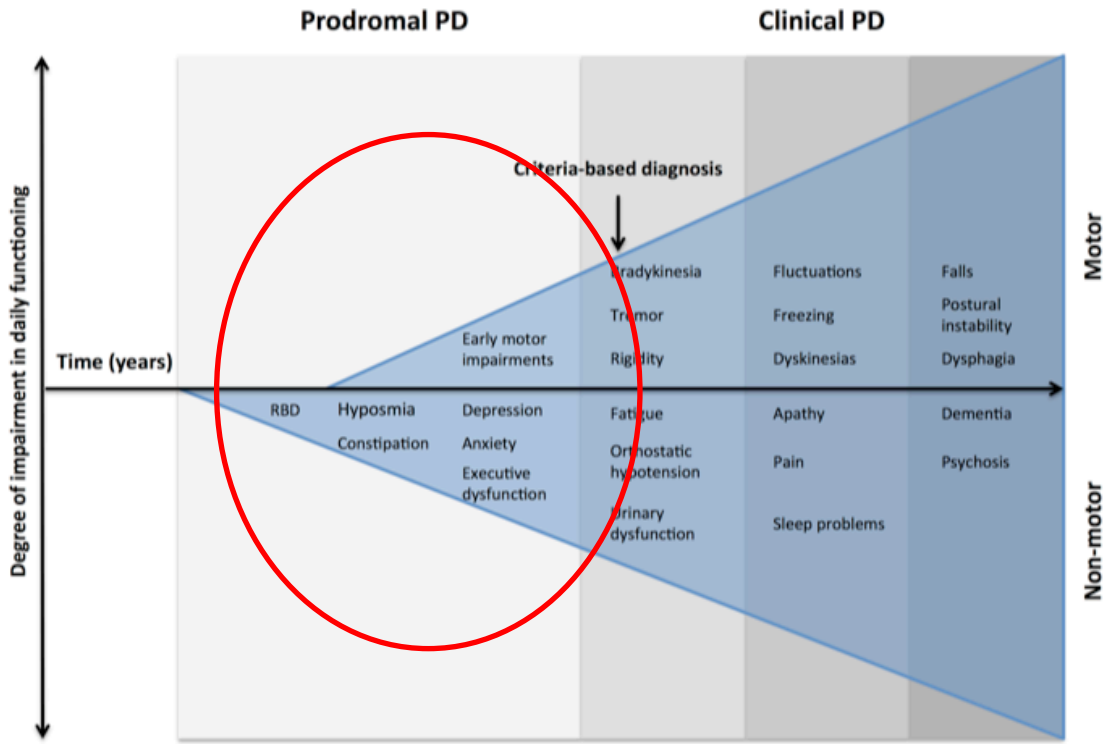
Ambroxol

- Phase IIa ongoing
- 20 GBA-positive patients
- Available over the counter (anti-mucolytic)
- Shown in cell culture and animal models to increase glucocerebrosidase activity and reduce alpha-synuclein aggregation

DNL201 (LRRK2 inhibitor)

- Phase Ib ongoing
- LRRK2 mutation carriers
- Phase 1 dose escalation study achieved adequate LRRK2 inhibition at doses that were safe and well tolerated

Myth 2: “PD presents with movement symptoms”



Breen et al, Brain 2017

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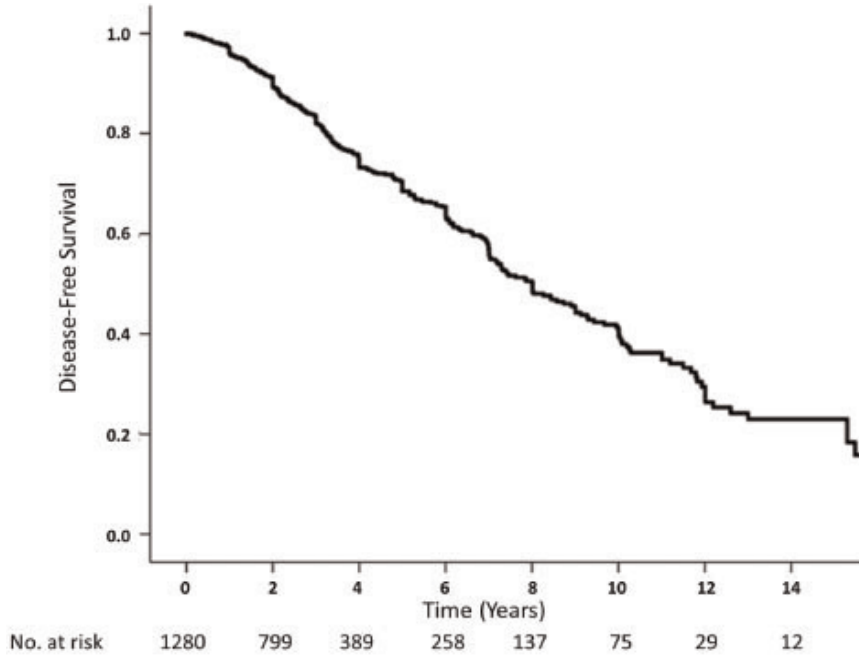
RBD as early marker of Parkinson's



At 12 years, three-quarters of patients had converted to parkinsonism (PD = 52%, MSA = 4.5%) or dementia (DLB = 43.5%)

Postuma et al, Brain 2019

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Myth 3: “There is no value in MR brain imaging”

Parkinson’s disease in adults

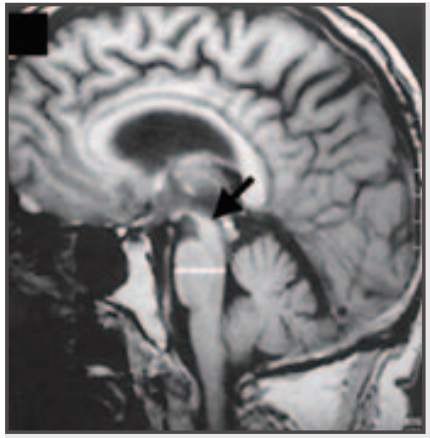
NICE guideline [NG71] Published date: July 2017 Uptake of this guidance

Structural MRI

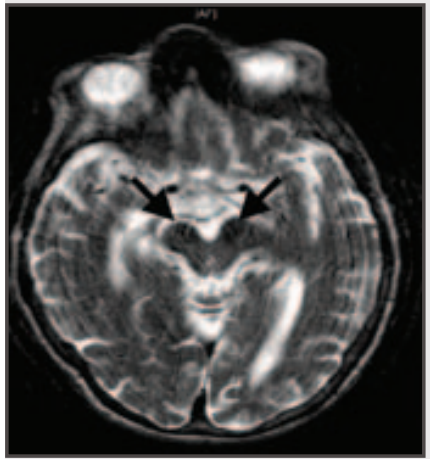
1.2.9 Do not use structural MRI to diagnose Parkinson's disease. **[2006, amended 2017]**

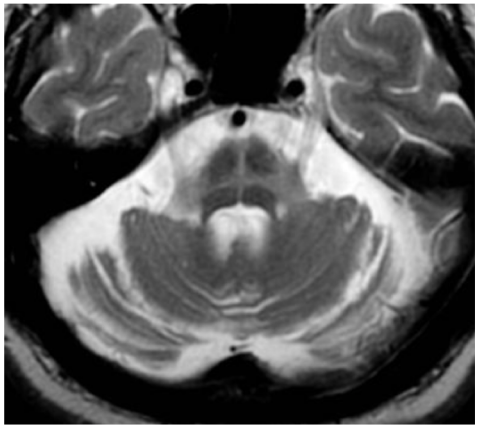
1.2.10 Structural MRI may be considered in the differential diagnosis of other parkinsonian syndromes. **[2006]**

Rationale for MRI

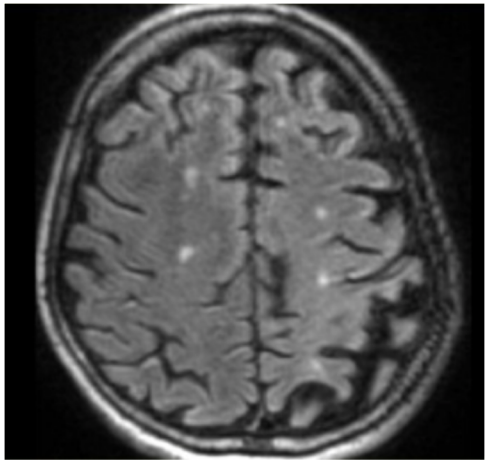


PSP





MSA



CBS

Breen et al, BMJ 2011

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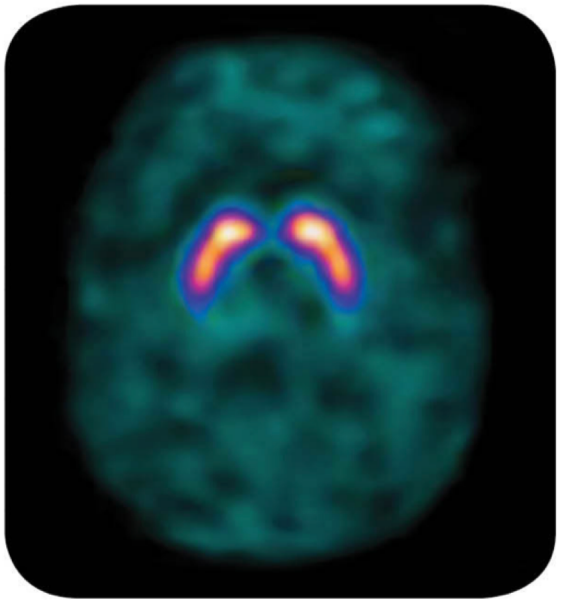
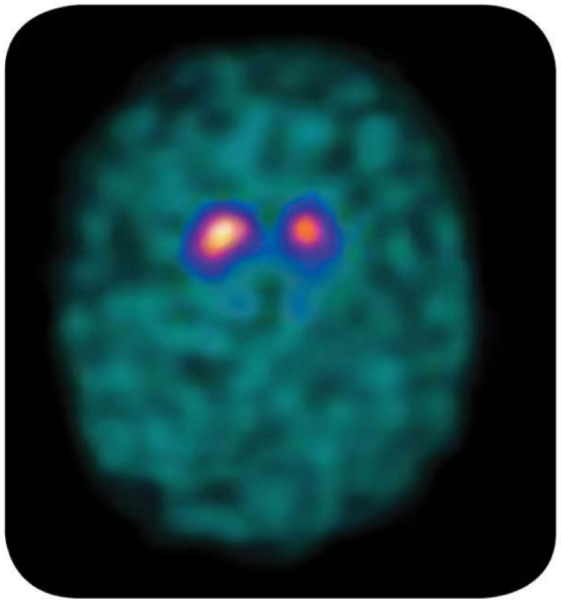
Myth 4: “DaT scan has replaced clinical acumen anyway”

Normal scan — Inconsistent with a parkinsonian syndrome



DaTscan will be distributed in the striata and appear as mirrored comma or crescent shapes if dopaminergic neurons are intact or not affected[1,4]

Abnormal scan — Consistent with a parkinsonian syndrome



A decrease in DaTscan activity will result in period or oval shapes and reduced image intensity on one or both sides[1,4]

Limitations

Qualitative report (‘equivocal scan’)

Does not distinguish idiopathic PD from atypical parkinsonian syndromes

False negatives in very early disease (especially tremor-dominant cases)

Some medications interfere with ligand binding

- *Increased binding*: Most anticholinergics, adrenergic drugs
- *Reduced binding*: Certain opiates (fentanyl), sertraline, benztropine, modafinil, cocaine, amphetamines
- ?Cigarette smoking

When can a DAT scan useful?

Drug-induced parkinsonism vs. degenerative parkinsonism

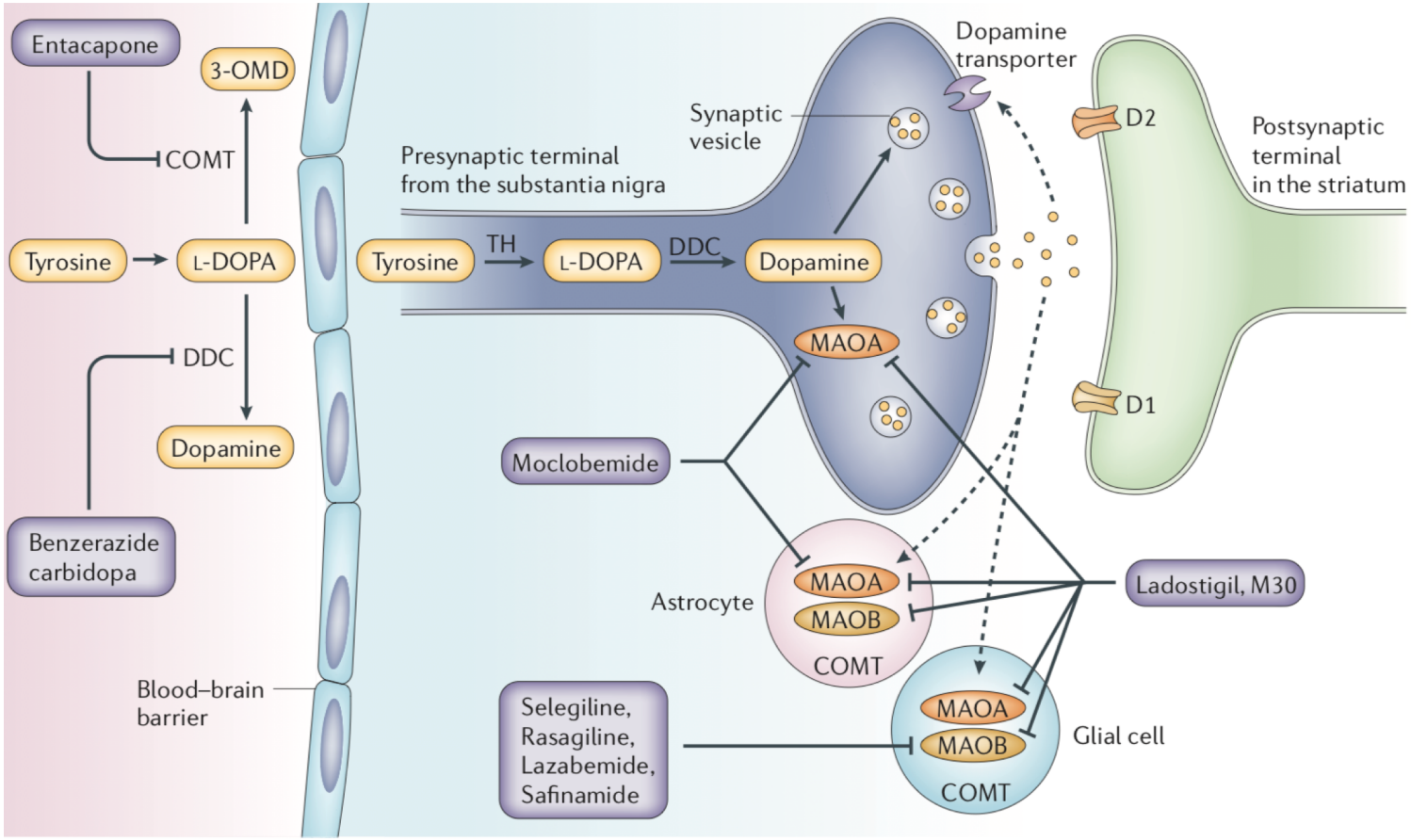
Essential or dystonic tremor with prominent rest tremor (or other soft neurological signs)

Functional overlay ++

?Poor response to levodopa

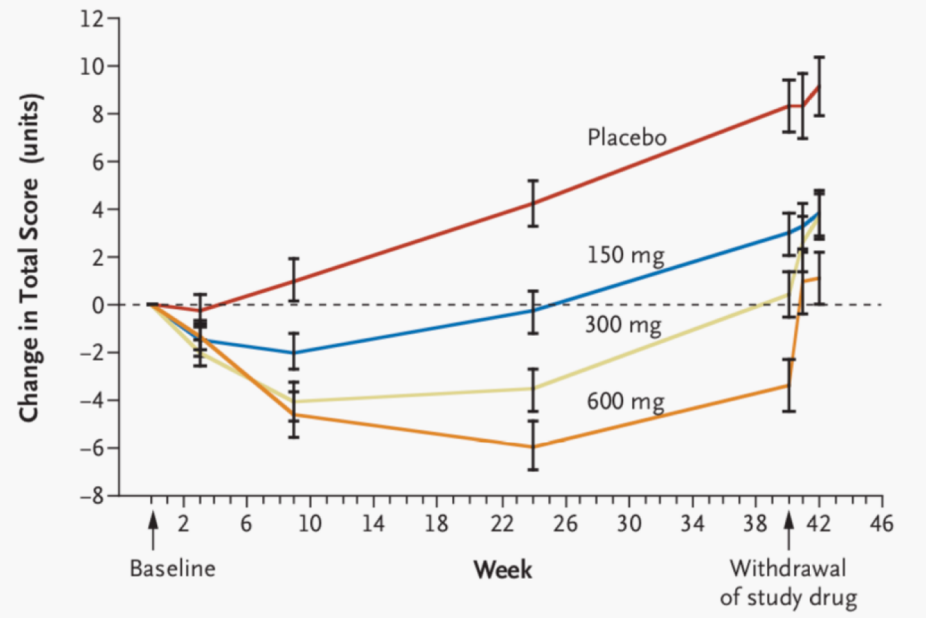
?Very early parkinsonism (especially as we enter an era of DMT trials)

Myth 5: “Levodopa only works for 5 years”



Youdim et al, Nat Rev Neurisci 2006

ELLDOPA study



All levodopa dosages led to improved motor function after washout period

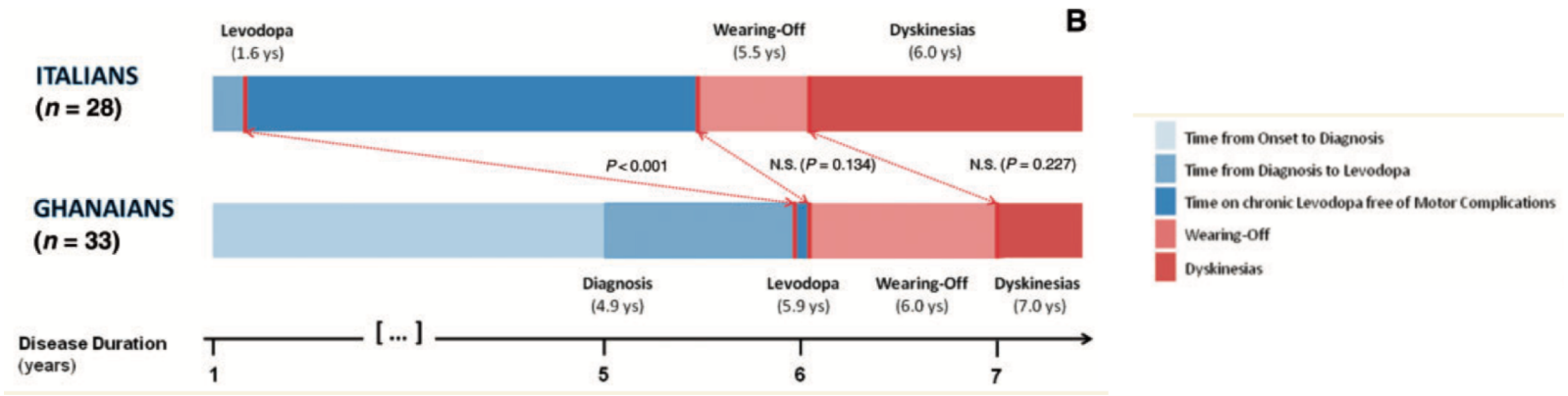
13% vs. 16% vs. 18% vs. 30% reported OFF symptoms at the end of the study

Greater reduction in DAT binding in levodopa-treated patients

Parkinson Study Group, NEJM 2004

Era of levodopa-sparing strategies

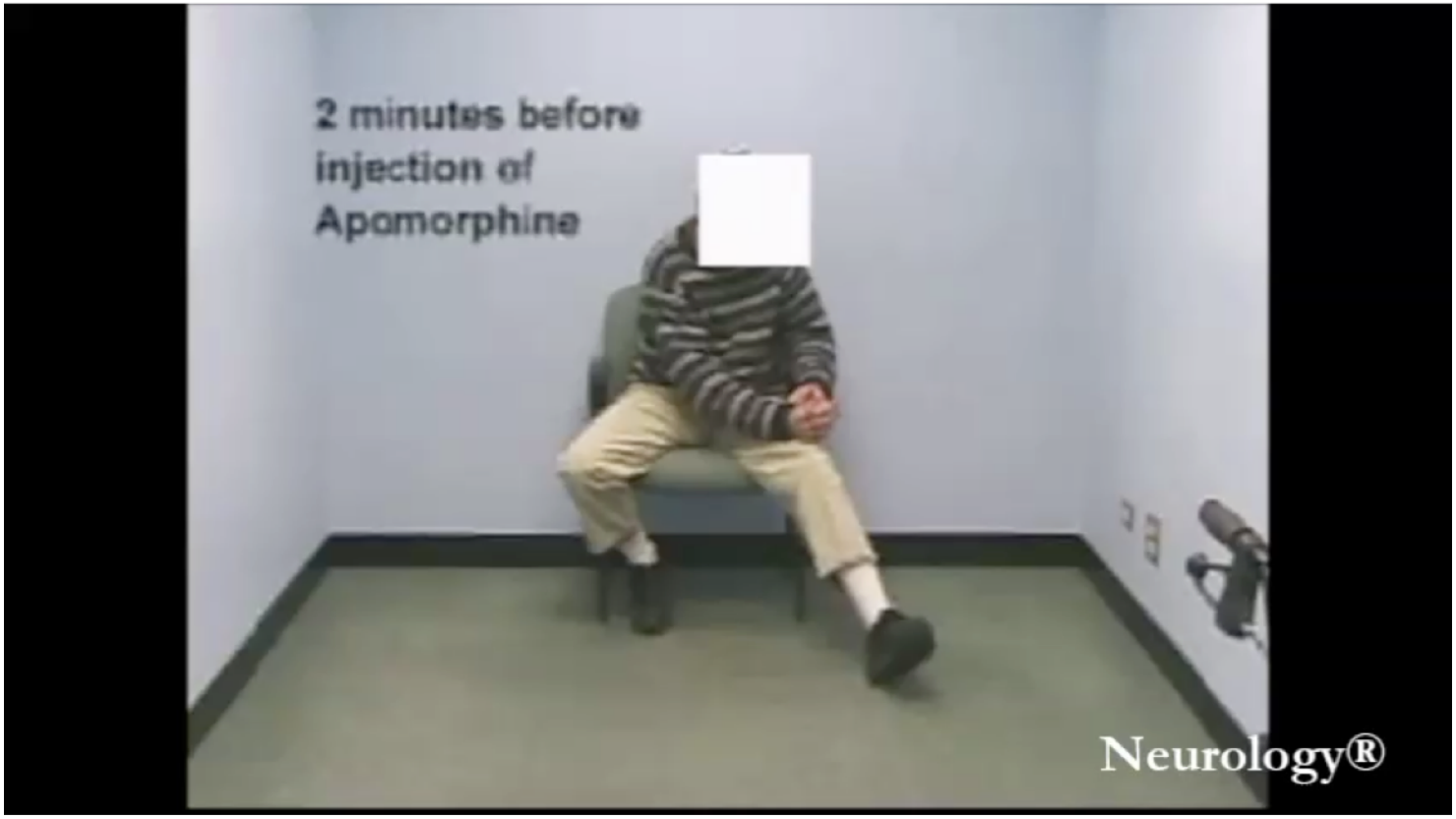
Several large randomised trials (including PD MED) reported reduction in dyskinesias with early dopamine agonist use, however follow-up studies have shown onset of dyskinesias at the same time/severity once levodopa added



Move away from dopamine agonists, particularly given their side effects (daytime sleepiness, impulse control behaviours, cognitive)

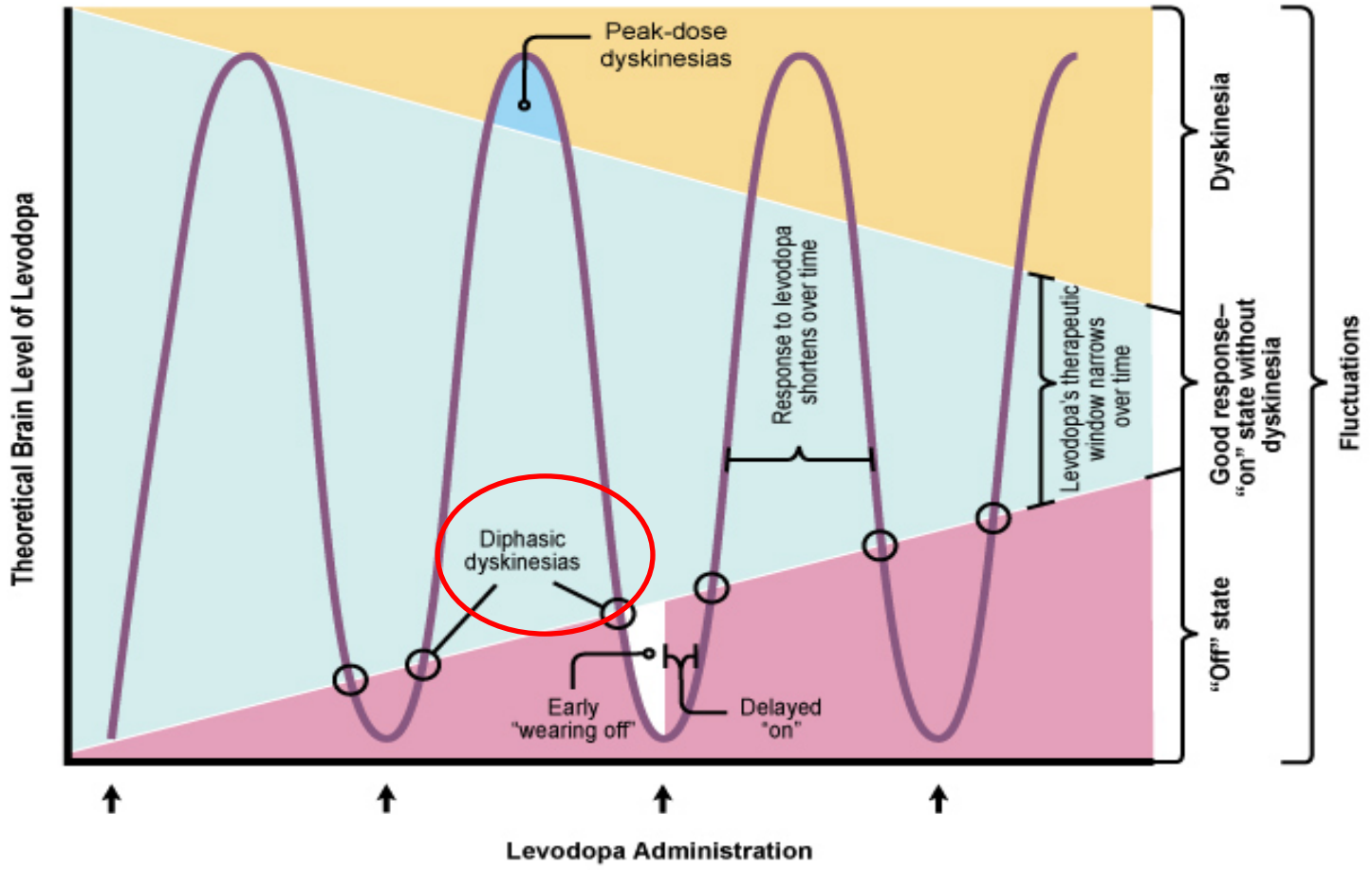
PDMED, Lancet 2014
Cilia et al, Brain 2014

Myth 6: “All dyskinesias are caused by too much medication”

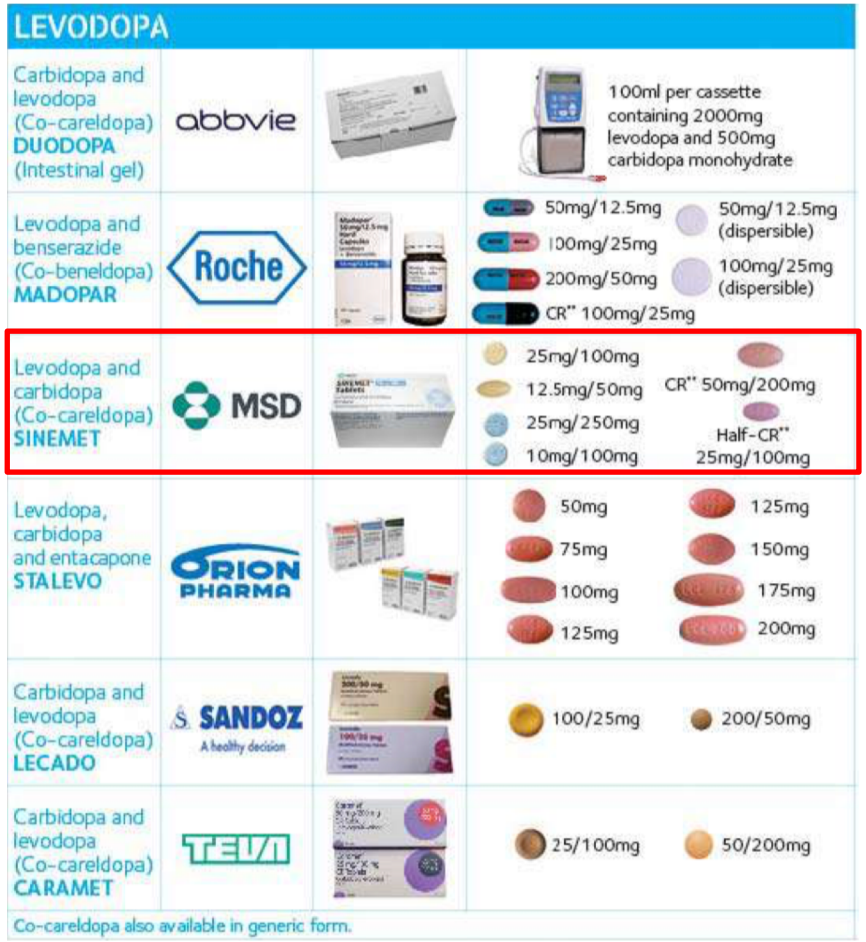


Metman et al, Neurology 2017

Diphasic dyskinesias



Myth 7: “Sinemet 10/100 is a lower dose than Sinemet 25/100”



LEVODOPA			
Carbidopa and levodopa (Co-careldopa) **DUODOPA** (Intestinal gel)	abbvie		100ml per cassette containing 2000mg levodopa and 500mg carbidopa monohydrate
Levodopa and benserazide (Co-beneldopa) **MADOPAR**	Roche		50mg/12.5mg; 50mg/12.5mg (dispersible); 100mg/25mg; 100mg/25mg (dispersible); 200mg/50mg; CR** 100mg/25mg
Levodopa and carbidopa (Co-careldopa) **SINEMET**	MSD		25mg/100mg; CR** 50mg/200mg; 12.5mg/50mg; 25mg/250mg; Half-CR** 25mg/100mg; 10mg/100mg
Levodopa, carbidopa and entacapone **STALEVO**	ORION PHARMA		50mg; 125mg; 75mg; 150mg; 100mg; 175mg; 125mg; 200mg
Carbidopa and levodopa (Co-careldopa) **LECADO**	SANDOZ A healthy decision		100/25mg; 200/50mg
Carbidopa and levodopa (Co-careldopa) **CARAMET**	TEVA		25/100mg; 50/200mg

Co-careldopa also available in generic form.

“sine” (without) “eme” (vomit)

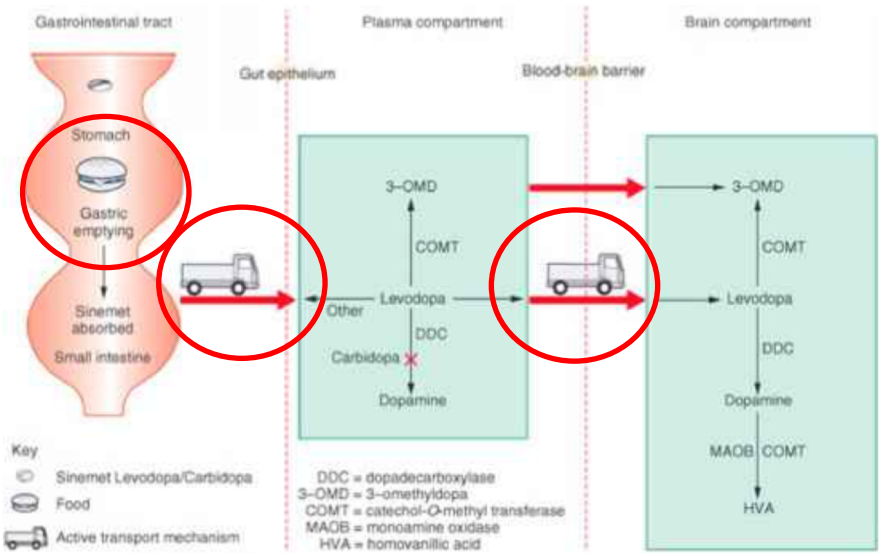
The 2nd number is the levodopa dosage

The 1st number is the carbidopa dosage (which prevents peripheral breakdown of levodopa)

No difference between Madopar and Sinemet

No difference (apart from cost) in generic or branded

Myth 8: “Levodopa should be taken with food”



Levodopa competes with large, neutral amino acids for absorption into bloodstream and brain

Food delays gastric emptying and causes degradation of levodopa in the stomach (“delayed ONs” or “dose failures”)

Some patients have additional gastroparesis (autonomic neuropathy)

Take away from meals if possible
(30 minutes before or 60 minutes after)

Myth 9: “MAO-B inhibitors can never be prescribed with SSRIs”

Theoretical risk of serotonin syndrome

- Clonus (limbs or ocular)
- Increased tone or reflexes
- Tremor or myoclonus
- Agitation
- Excessive sweating
- Hyperthermia

Selectivity of MAO inhibition

MAO exists in two isoforms: MAO-A (mainly in body) and MAO-B (mainly in brain)

- MAO-A inhibition reduces the metabolism of both serotonin and noradrenaline, whereas MAO-B does not
- MAO-B prevents the extracellular breakdown of dopamine in the brain, and does not interfere with above (unless high doses are used)
- Selegiline and rasagiline at PD doses are selective MAO-B inhibitors

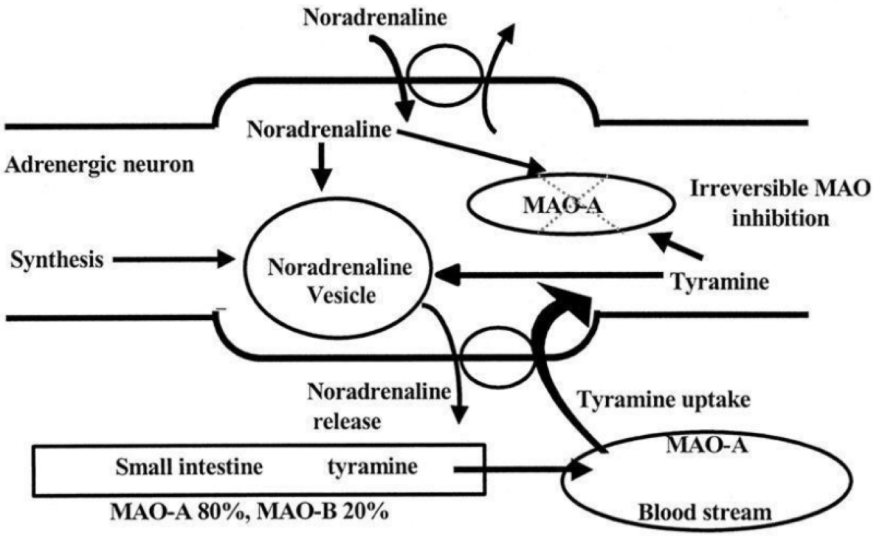
Interaction between Monoamine Oxidase B Inhibitors and Selective Serotonin Reuptake Inhibitors

12 reported cases of serotonin syndrome in total (5 from MEDLINE search, 2 submitted to FDA, 4 from survey of PSG investigators

Aboukharr et al, Can J Hosp Pharm 2018

Myth 10: “Taking MAO-B inhibitor increases the risk of cheese reaction”

Taking some MAO-I along with foods high in tyramine (aged cheese, red wine, herring) carries a risk of uncontrolled hypertension



Selegiline 10mg daily and Rasagiline 1mg daily are extremely unlikely to cause this

Other things about Selegiline

Patients taking selegiline may test positive for amphetamines on toxicology screening

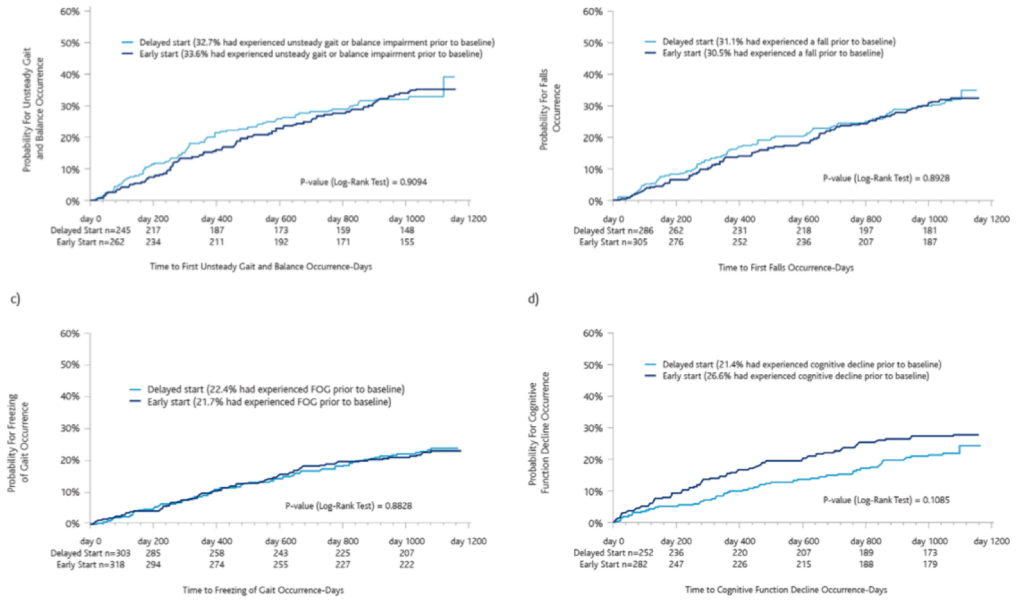
Amphetamine-like metabolites are probably the cause of agitation, insomnia and hallucinations in susceptible individuals (hence avoid at night)

Rasagiline dose not have the same amphetamine-like by-products

Myth 11: “Rasagiline slows disease progression”

Attenuation of Disease progression with Azilect™ Given Once Daily (ADAGIO)

- Initial 18 month prospective, double-blind, delayed-start study
- Primary analysis reported a benefit of early-start with Rasagiline 1mg but not 2mg
- 2 years after trial completion, a 3-year follow-up study was initiated (1mg and 2mg pooled)



Rascol et al, MDJ 2016

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Myth 12: “There is nothing else that patients can do to influence their disease”

Potential benefits of exercise

Box 1 Jane's thoughts about exercise

Exercise has radically improved my life with Parkinson's. Regular and increasingly intensive exercise has had a significant effect on my symptoms.

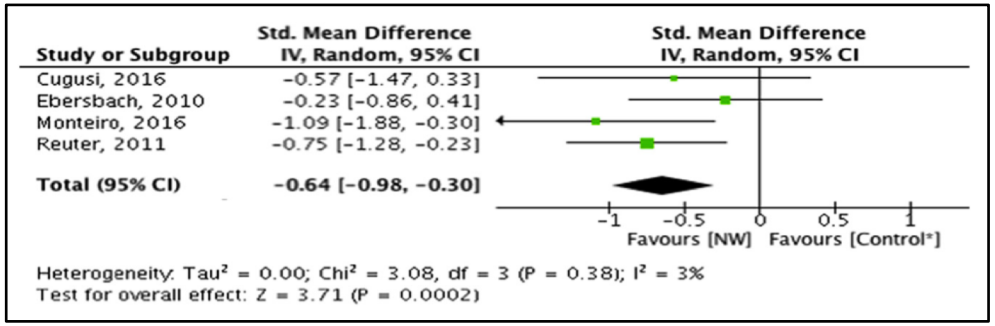
Exercise has reduced my adverse motor symptoms. In some ways, more significantly, it has kept me positive emotionally. I feel good about my body again. I believe I am doing something to control my condition. Ten years after diagnosis I can confidently abseil down a waterfall and hike up 3000 feet below Mont Blanc!

I have only needed a small increase in my Madopar dose over the 5 years I have been exercising.

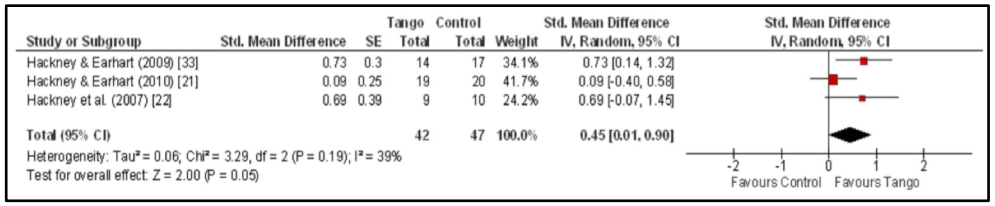
My only regret is that I wish I had started exercising to this level immediately after diagnosis.

Ramaswamy et al, Practical Neurol 2018

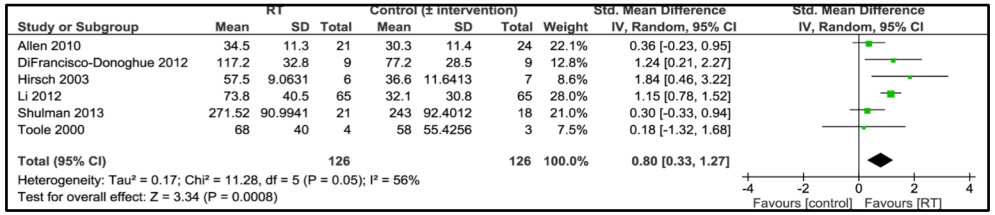
Types of exercise



Nordic walking and UPDRS



Argentine tango and balance



Resistance training and muscle strength

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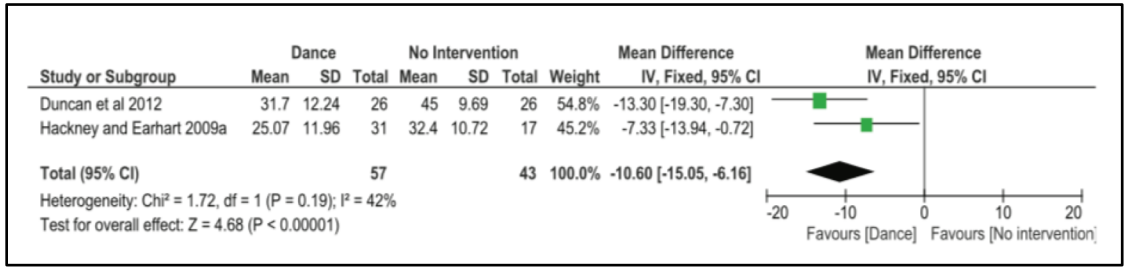
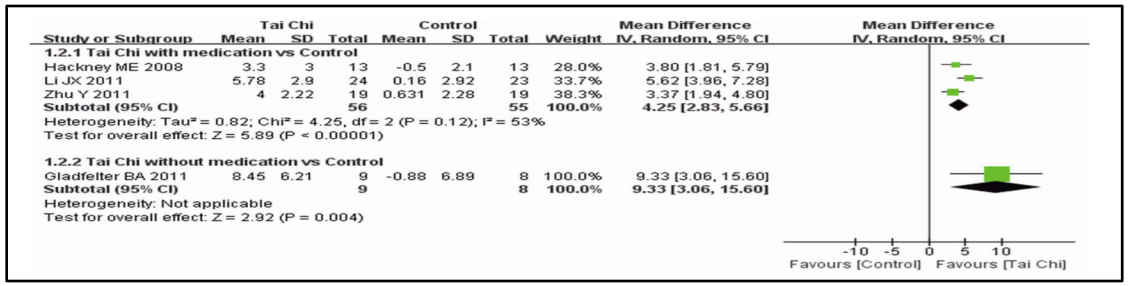
Types of exercise



Dance and UPDRS



Tai Chi and balance

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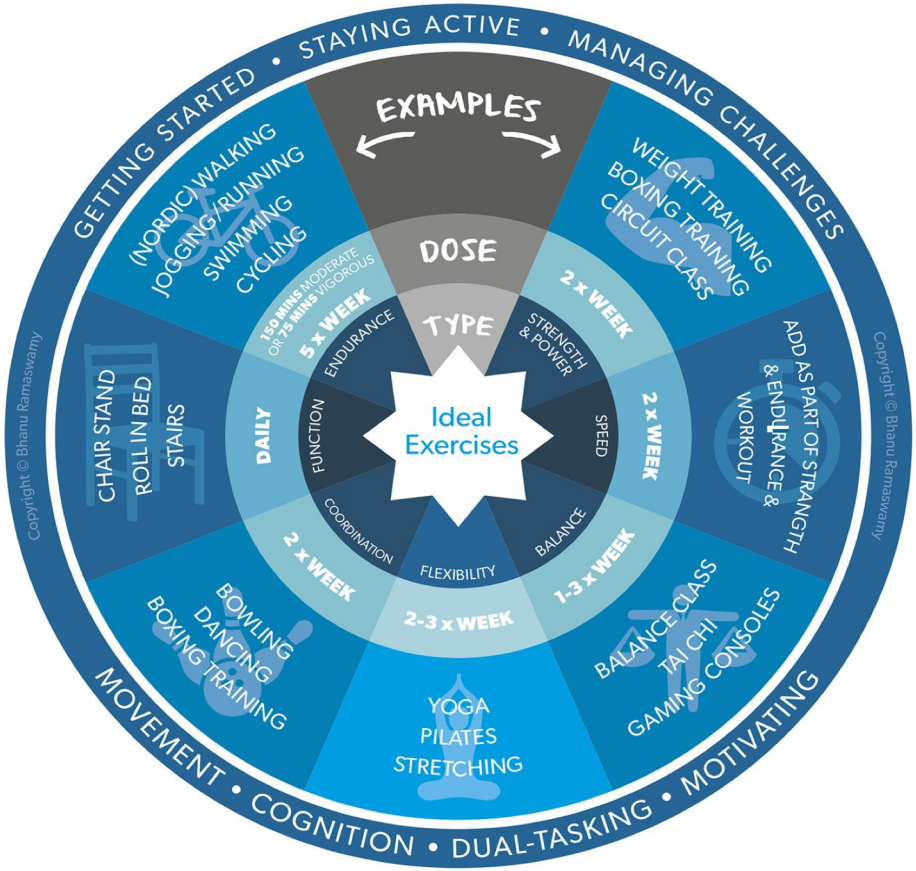
Creating an exercise regimen



Regular Activities
Adaptive Yoga
Aquatherapy
Art group
Carers Support Group
Dance for Parkinson's Scotland
Gentle Exercise
Edinburgh Young Parkinson's Support Group
Chess
Indoor Bowling
Nordic Walking for Parkinson's
Parkinson's Group at Thistle
Pilates for Parkinson's
Quality of Life Group
Singing4fun with Parkinson's
Swimming
Tai Chi for Parkinson's
Tandem and Other Cycling
Wu-style Tai Chi
Young Parkinson's Carers Support Group

www.edinburghparkinsons.org

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Myth 13: “There are no effective treatments for gait freezing”

Try altering levodopa dose ✓

- Amantadine
- Methylphenidate

✗

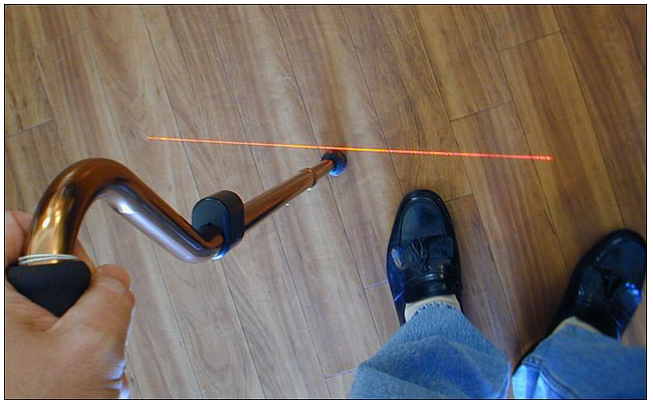
Physiotherapy

- External cues (marching, humming, singing, (stepping over imaginary line, laser projector)
- Internal cues and motor imagery
- Change in balance requirements
- Treating anxiety
- Different walking styles

Occupation therapy

- Home adjustment

✓



Nonnekes et al, Lancet Neurol 2015

What about spinal cord stimulation?

Parkinson's results beyond researchers' wildest dreams

Spinal Cord Stimulation Therapy for Gait Dysfunction in Advanced Parkinson's Disease Patients

Olivia Samotus, MSc,[1,2] Andrew Parrent,[1,2] and Mandar Jog, MD[1,2*]

[1]*London Health Sciences Centre – Lawson Health Research Institute, Department of Clinical Neurological Sciences, London, Ontario, Canada*
[2]*University of Western Ontario, Schulich School of Medicine and Dentistry, London, Ontario, Canada*

Samotus et al, MDJ 2018

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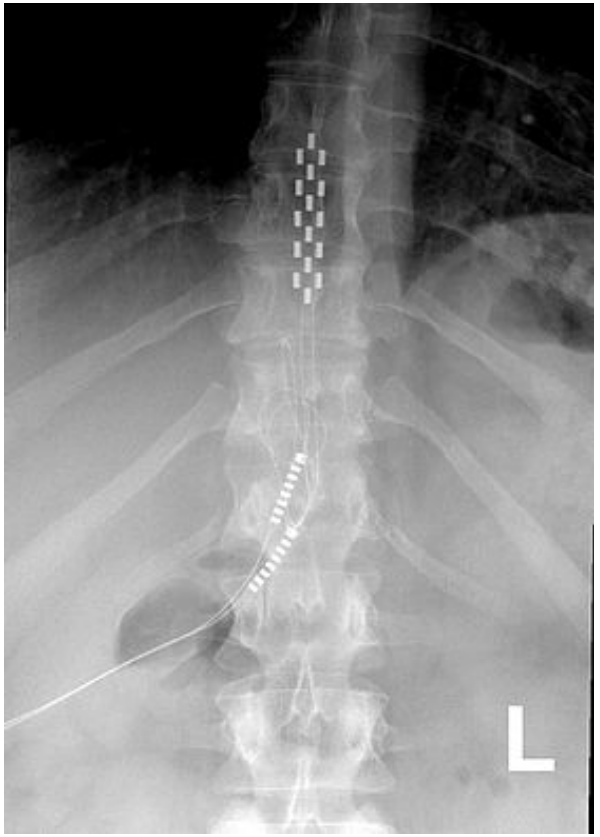
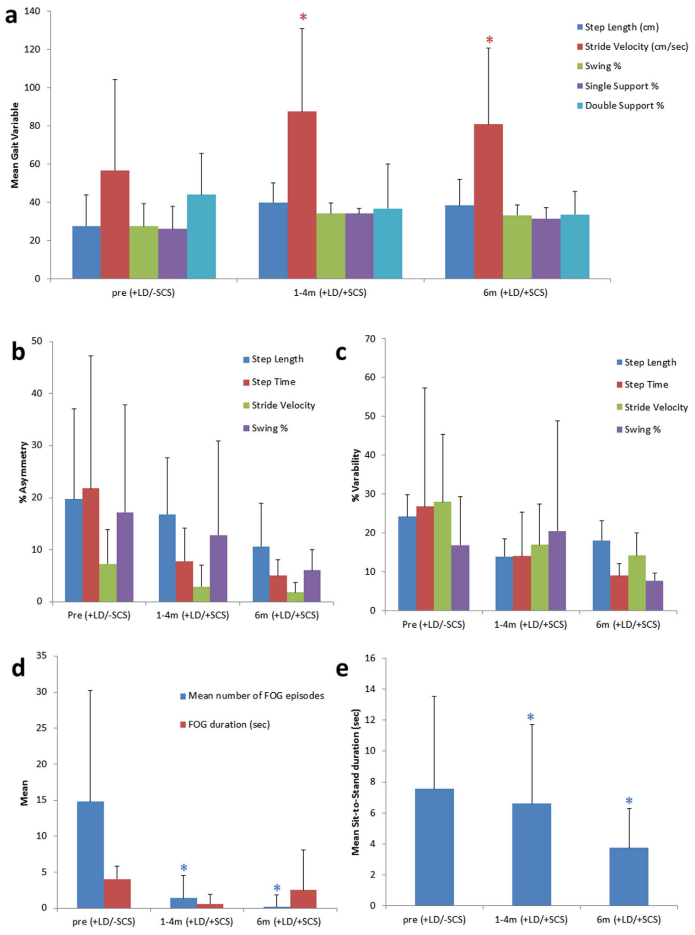
What about spinal cord stimulation?

Open-label, exploratory, non–randomised pilot study

- 5 male PD patients, broad inclusion criteria (all had falls and FOG)
- Implantation of two electrodes in medial epidural space at T8-10 spinal segments
- No adverse events related to surgery
- 6 months of dorsal spinal cord stimulation (11 frequency and pulse width combinations tested in blinded fashion)
- Best stimulation setting chosen by gait analysis (no defining trends)
- All patients improved in terms of UPDRS and step length
- Improvements also seen in activities-specific balance confidence scale (ABC), but not FOG-Q or PDQ-8



What about spinal cord stimulation?



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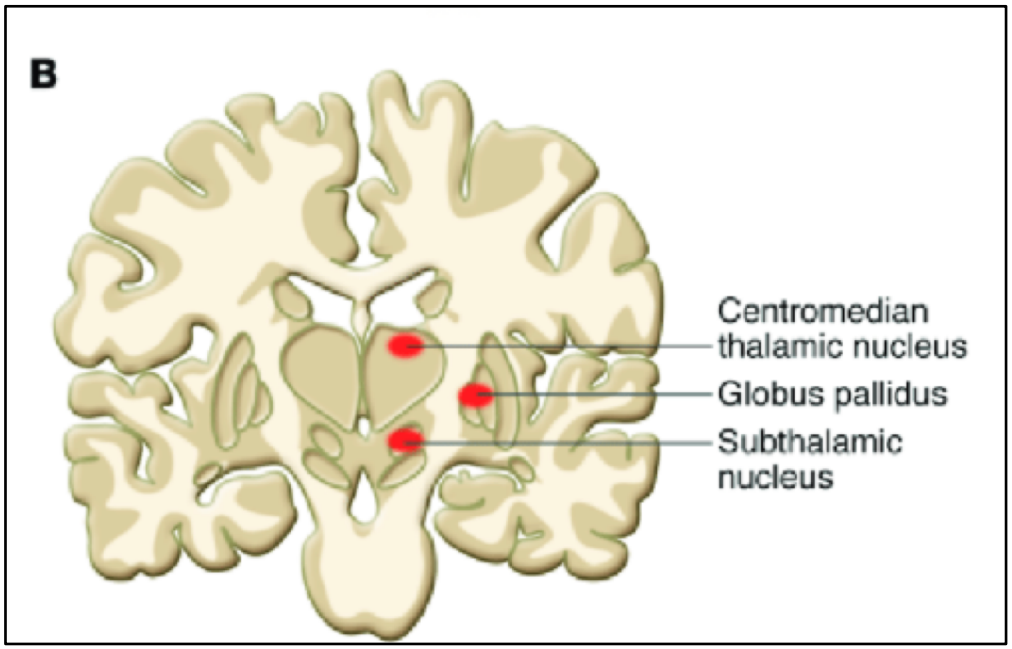
Myth 14: “DBS is always the last resort”



EARLYSTIM TRIAL

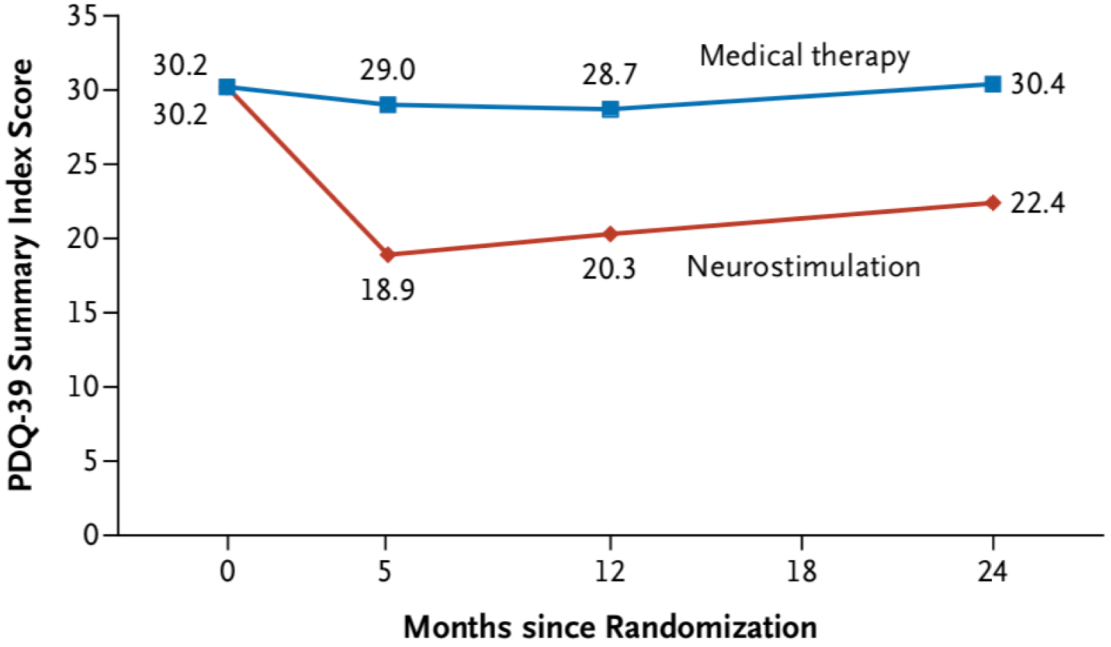
Effect of bilateral STN-DBS in PD with early motor fluctuations (within 3 years)

Compared with Best Medical Therapy

PDQ-39 (QoL) as the primary outcome measure

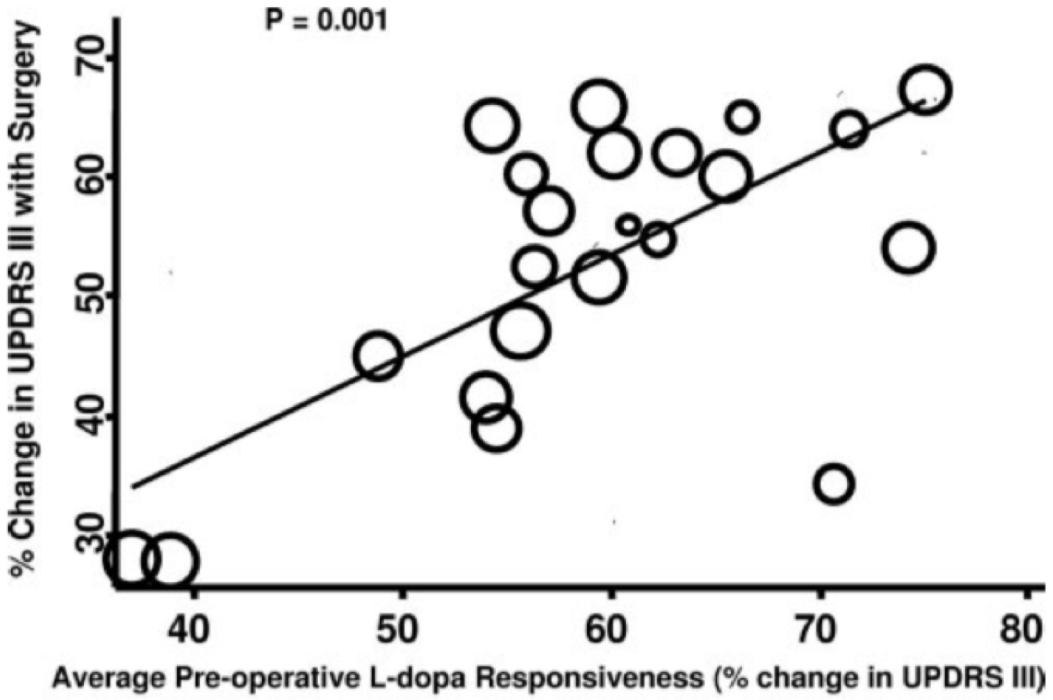
Schuepach et al, NEJM 2013

EARLYSTIM Results



- 25% improvement in PDQ-39 in DBS group
- 26% and 53% improvement in UPDRS-III in medication 'ON' and 'OFF' states
- Improvement in UPDRS-IV by 61%

Myth 15: “DBS should be given for symptoms that do not respond to levodopa”



Kleiner-Fisman et al, MDJ 2006

Myth 16: “Never give antipsychotics in PD”

If needed, favour second generation (atypical) antipsychotic such as quetiapine

Parkinson’s disease in adults

NICE guideline [NG71] Published date: July 2017 Uptake of this guidance

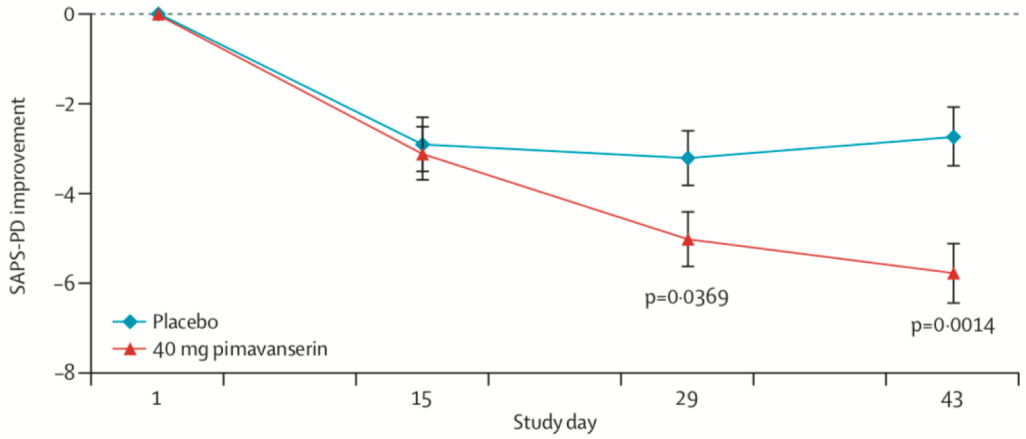
1.5.16 Consider quetiapine[4] to treat hallucinations and delusions in people with Parkinson's disease who have no cognitive impairment. **[2017]**

1.5.17 If standard treatment is not effective, offer clozapine to treat hallucinations and delusions in people with Parkinson's disease. Be aware that registration with a patient monitoring service is needed. **[2017]**

Pimavanserin (Nuplazid™) for PD psychosis

Randomised, placebo-controlled phase 3 study of pimavanserin 40mg once daily vs. placebo

- Selective serotonin 5HT-2A inverse agonist
- 199 patients studied over 6 weeks (2-week run-in period with psychotherapy)
- 52 centres in US and Canada
- **Inclusion**: Aged >40, psychotic symptoms for >1 month (delusions and/or hallucinations), MMSE >20, stable drug dosages



37% vs. 14% improvement

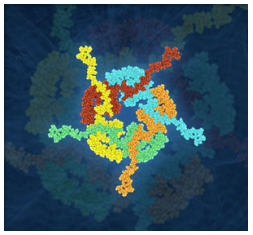
Improved caregiver burden and sleep

Cummins et al, Lancet 2014

The University of Edinburgh
Edinburgh Neuroscience

CCBS
Centre for Clinical Brain Sciences

Myth 17: “There are never going to be any new PD therapies”



Alpha-synuclein vaccines (passive)

BIIB054 (Biogen/Neurimmune)
Phase 2 (SPARK) ongoing, multicentre

Prasinezumab (PRX002) (Prothena/Roche)
Phase 2 (PASADENA) ongoing, multicentre

MEDI1341 (Astrazeneca/Takeda)
Phase 2 (PASADENA) ongoing, Dallas

Alpha-synuclein vaccines (active)

AFFITOPE® PD01A (Affiris)
Phase 1 ongoing

Anti-synuclein compounds

NPT200-11/ UCB0599 (Neuropore/UCB)
Phase 1b ongoing

NPT088 (Proclara)
On hold, testing in AD first

Drug repurposing – Exenatide

- GLP-1 receptor agonist (synthetic version of exendin-4)
- Discovered in the saliva of the Gila monster
- Used since 2005 to treat diabetes, causes insulin to be released
- Animal studies indicate that the drug may be neuroprotective

Exenatide and the treatment of patients with Parkinson's disease

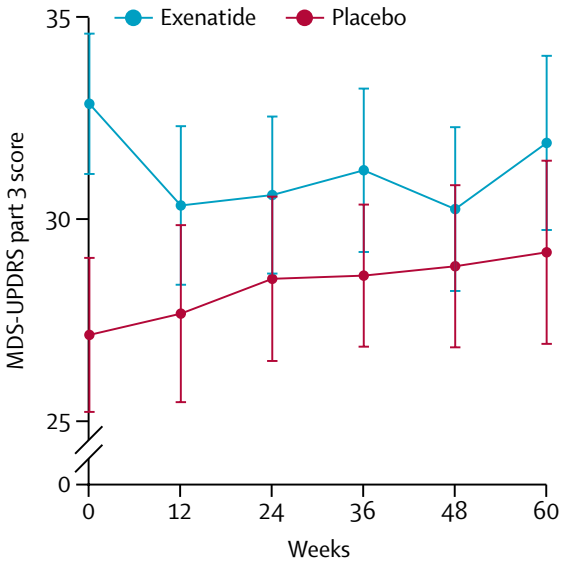
Iciar Aviles-Olmos,[1] John Dickson,[2] Zinovia Kefalopoulou,[1] Atbin Djamshidian,[3] Peter Ell,[2] Therese Soderlund,[2] Peter Whitton,[4] Richard Wyse,[5] Tom Isaacs,[5] Andrew Lees,[3] Patricia Limousin,[1] and Thomas Foltynie[1]

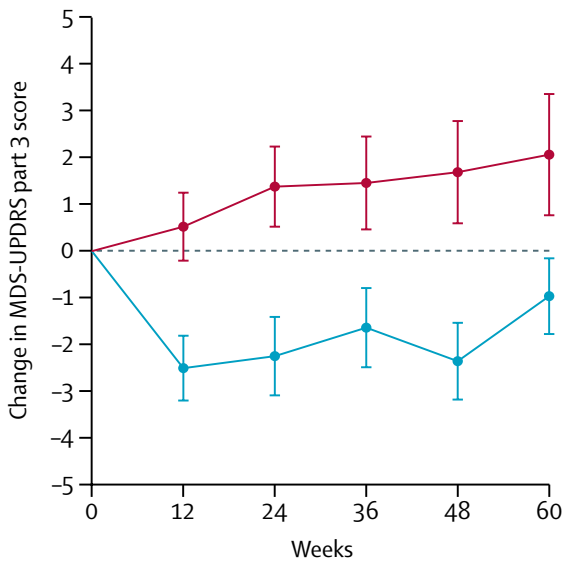
Aviles et al, JCI 2013

Drug repurposing – Exenatide

Randomised, placebo-controlled, phase 2 study of exenatide 2mg vs. placebo

- Weekly subcutaneous injections over 48 weeks, followed by 12 week washout
- PD patients with fluctuations
- Single centre (UCL)
- On dopaminergic medications with wearing off symptoms





UPDRS-part 3 OFF score worsened by 2.1 points in placebo vs. improved by 1.0 in exenatide group

No difference in ON UPDRS scores

Side effects: Weight loss (2.6kg), injection site reactions, 1 patient discontinued due to amylasaemia

Athuda et al, Lancet 2014

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